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(21) International Application Number: PCT/EP96/00368 (22) International Filing Date: 26 January 1996 (26.01.96) (30) Priority Data: <table border="0"> <tr> <td>9502052.5</td> <td>2 February 1995 (02.02.95)</td> <td>GB</td> </tr> <tr> <td>9508327.5</td> <td>25 April 1995 (25.04.95)</td> <td>GB</td> </tr> <tr> <td>9508967.8</td> <td>3 May 1995 (03.05.95)</td> <td>GB</td> </tr> <tr> <td>9516845.6</td> <td>17 August 1995 (17.08.95)</td> <td>GB</td> </tr> <tr> <td>9517542.8</td> <td>26 August 1995 (26.08.95)</td> <td>GB</td> </tr> <tr> <td>9518574.0</td> <td>12 September 1995 (12.09.95)</td> <td>GB</td> </tr> </table> (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): GASTER, Laramie, Mary [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). WYMAN, Paul, Adrian [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). MULHOLLAND, Keith, Raymond [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		9502052.5	2 February 1995 (02.02.95)	GB	9508327.5	25 April 1995 (25.04.95)	GB	9508967.8	3 May 1995 (03.05.95)	GB	9516845.6	17 August 1995 (17.08.95)	GB	9517542.8	26 August 1995 (26.08.95)	GB	9518574.0	12 September 1995 (12.09.95)	GB	DAVIES, David, Thomas [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). DUCKWORTH, David, Malcom [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). FORBES, Ian, Thomson [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). JONES, Graham, Elgin [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). (74) Agent: SUMMERSELL, Richard, John; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
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(54) Title: INDOLE DERIVATIVES AS 5-HT RECEPTOR ANTAGONIST																					
(57) Abstract The invention relates to heterocyclic compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders such as anxiety.																					

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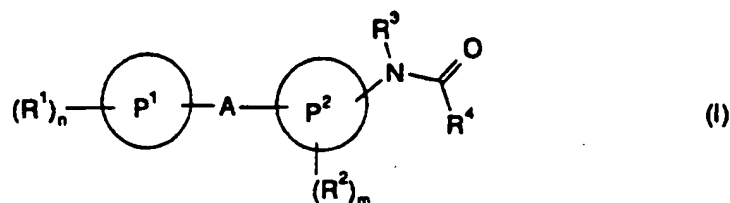
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Indole derivatives as 5-HT receptor antagonist

This invention relates to compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

WO 94/04533 (SmithKline Beecham plc) describes indole and indoline derivatives which are described as possessing 5HT_{2C} receptor antagonist activity. A structurally distinct class of compounds has now been discovered, which have been found to have 5HT_{2C} receptor antagonist activity. Certain compounds of the invention also exhibit 5HT_{2B} antagonist activity. 5HT_{2C/2B} receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



wherein:

P¹ and P² are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

A is a bond, a chain of 1 to 5 atoms optionally substituted by C₁₋₆ alkyl or A is an optionally substituted phenyl or an optionally substituted 5- to 7-membered

heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

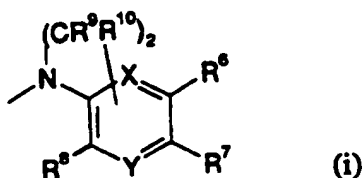
R¹ and R² groups are each independently hydrogen, C₁₋₆ alkyl optionally substituted by NR¹²R¹³, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylthio, cyano, nitro, halogen, CF₃, C₂F₅, NR¹²R¹³, CONR¹²R¹³, NR¹²COR¹³, S(O)_pNR¹²R¹³, CHO, OCF₃,

SCF₃, COR¹⁴, CH₂OR¹⁴, CO₂R¹⁴ or OR¹⁴ where p is 1 or 2 and R¹², R¹³ and R¹⁴ are independently hydrogen, C₁₋₆ alkyl, optionally substituted aryl or optionally substituted arylC₁₋₆alkyl;

n and m are independently 0, 1 or 2;

5 R³ is hydrogen or C₁₋₆ alkyl;

R⁴ is a group of formula (i):



10 in which:

X and Y are both nitrogen, one is nitrogen and the other is carbon or a CR⁵ group or one is a CR⁵ group and the other is carbon or a CR⁵ group;

R⁵, R⁶, R⁷ and R⁸ groups are independently hydrogen, C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl, C₃₋₆

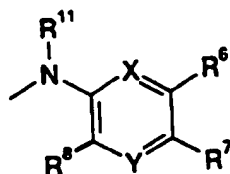
15 cycloalkylC₁₋₆alkoxy, C₂₋₆ alkynyl, C₃₋₆ cycloalkyloxy, C₃₋₆ cycloalkyl-C₁₋₆ alkyl, C₁₋₆ alkylthio, C₃₋₆ cycloalkylthio, C₃₋₆ cycloalkyl-C₁₋₆ alkylthio,

C₁₋₆alkoxy, hydroxy, halogen, nitro, OCF₃, SCF₃, SO₂CF₃, SO₂F, formyl, C₂₋₆ alkanoyl, cyano, optionally substituted phenyl or thienyl, NR¹²R¹³, CONR¹²R¹³ or

20 CO₂R¹⁴ where where R¹², R¹³ and R¹⁴ are as defined for R¹; or R⁶ and R⁷ form part of an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring;

R⁹ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl; or

R⁴ is a group of formula (ii):

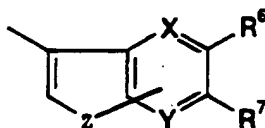


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in which X and Y are both nitrogen, one is nitrogen and the other is a CR⁵ group or X and Y are both CR⁵ groups and R⁵, R⁶, R⁷ and R⁸ are as defined in formula (I); and

30 R¹¹ is hydrogen or C₁₋₆ alkyl, or

R⁴ is a group of formula (iii):



(iii)

in which R^6 , R^7 , X and Y are as defined in formula (i) and Z is O, S, CH_2 or NR^{15}
 5 where R^{15} is hydrogen or C_{1-6} alkyl.

C_{1-6} Alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably A is a bond or a chain of 1 to 5 atoms optionally substituted by C_{1-6} alkyl. Examples of such chains include $(CH_2)_pX$ or $X(CH_2)_p$ where p is 1 to 4
 10 and X is CO, O, $S(O)_x$ where x is 0 to 2 or A is NR, CONR, NRCO, NRCONR, CO, CH(OH), C_{1-6} alkyl, CH=CH, CH=CF, CF=CF, O, $S(O)_x$ where x is 1 or 2, NR, or $NRSO_2$ where R is hydrogen or C_{1-6} alkyl. Preferably A is a bond or a group CH_2O , OCH_2 , or O.

Suitably A is an optionally substituted phenyl group or an optionally
 15 substituted 5- or 6-membered heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur. Preferably A is thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidyl or pyrazinyl. Most preferably A is thiazolyl. Optional substituents when A is a phenyl or a heterocyclic group include those groups R^1 and R^2 listed above

The urea moiety can be attached to a carbon or any available nitrogen atom of the ring P^2 , preferably it is attached to a carbon atom. Suitable moieties when the rings P^1 and P^2 are 5-membered aromatic heterocyclic rings include isothiazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl and triazolyl. Suitable moieties when the rings P^1 and P^2 are 6-membered aromatic heterocyclic rings include, for example, pyridyl,
 25 pyrimidyl or pyrazinyl. Optional substituents for P^1 and P^2 groups include those groups R^1 and R^2 listed above

When A is a bond, P^1 is preferably phenyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl, preferably phenyl or pyridyl, in particular 3-pyridyl.

When A is a chain of 1 to 5 atoms, P^1 is preferably phenyl or pyridyl and P^2
 30 is preferably phenyl or pyridyl, in particular 3-pyridyl.

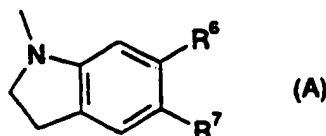
When A is an optionally substituted phenyl group or an optionally substituted 5- or 6-membered aromatic heterocyclic ring, P^1 is preferably phenyl or pyridyl and P^2 is preferably phenyl or pyridyl, in particular 3-pyridyl.

Preferably R^1 is hydrogen or methyl.

35 Preferably R^2 is hydrogen, halogen, methyl, CF_3 or OCF_3 .

Preferably R^3 is hydrogen.

Preferably R^4 is a group of formula (i). Preferably X and Y form part of a phenyl ring, that is to say one of X or Y is carbon and the other is a CH group or both of X and Y are CH groups. Most preferably R^4 is a group of formula (A):



5

in which R^6 and R^7 are as defined in formula (i).

Suitably R^6 and R^7 groups are independently hydrogen, C_{1-6} alkyl optionally substituted by one or more fluorine atoms for example CF_3 or C_2F_5 , C_{2-6} alkenyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyloxy, C_{3-6} cycloalkyl- C_{1-6} alkyl, C_{1-6} alkylthio, C_{3-6} cycloalkylthio, C_{3-6} cycloalkyl- C_{1-6} alkylthio, C_{1-6} alkoxy, hydroxy, halogen, nitro, CF_3 , C_2F_5 , OCF_3 , SCF_3 , SO_2CF_3 , SO_2F , formyl, C_{2-6} alkanoyl, cyano, optionally substituted phenyl or thienyl, $NR^{12}R^{13}$, $CONR^{12}R^{13}$ or CO_2R^{14} where R^{12} , R^{13} and R^{14} are as defined for R^1 ; or R^6 and R^7 form part of an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring. Examples of such rings include cyclopentane and dihydrofuran rings.

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Preferably R^6 is trifluoromethyl or halogen and R^7 is C_{1-6} alkoxy, in particular methoxy, C_{1-6} alkylthio, in particular methylthio or C_{1-6} alkyl in particular methyl.

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Suitably n and m are independently 0, 1 or 2. Preferably n and m are both 1.

Particular compounds of the invention include:

- 1-[(3-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[(4-Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline,
- 25 1-[(3-Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline,
- 1-[(3-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 1-[(4-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[(2-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[4-Methyl-3-(3-Pyridyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 30 1-[3-Fluoro-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[2-Fluoro-5-(3-pyridyl) phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethyl indoline,
- 1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methylthio-6-trifluoromethyl indoline,
- 1-[5-(3-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,

- 1-[5-(4-Trifluoromethylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[5-(4-Methylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[5-(2-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 5 1-[5-(3-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[5-(2-Pyrrolyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[5-(4-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[2-(3-Pyridyl)-thiazol-4-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[2-(2-Pyridyl)-thien-5-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 10 1-(3-Fluoro-5-(4-methyl-3-pyridyl)phenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
- 1-(5-(2,6-Difluorophenyl)-3-pyridylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
- 6-Chloro-5-methyl-1-(4-methyl-3-(pyrid-3-yl)-phenylcarbamoyl) indoline,
- 15 1-(4-Methyl-3-(pyrid-3-yl) phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl indoline,
- 1-(3-Fluoro-5-(pyrid-3-yl)phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl-indoline,
- 1-(4-Chloro-3-(pyrid-3-yl)phenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
- 20 5-Methoxy-1-(5-methyl-(1,2,4-oxadiazol-3-yl)-phenylcarbamoyl)-6-trifluoromethyl indoline,
- 1-[4-Methyl-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[5-Bromo-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 25 1-[4-*t*-Butyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 1-[4-Methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 1-[5-Fluoro-4-methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 1-[3-Bromo-4-methyl-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 30 1-[3-(4-Isoquinolyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[5-(4-Methyl-3-pyridyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 1-[6-(3-Pyridyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
- 35 1-[5-(2-Furyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
- 1-[2-(Pyrazinyl)-thiazol-4-ylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,
- 1-[3-(5-Pyrimidyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,
- 1-[3-(4-Methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,

- 1-[5-Ethyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 5-Methoxy-1-[5-phenyl-3-(pyrid-3-yl)phenylcarbamoyl]-6-trifluoromethyl indoline,
 6-Chloro-5-methyl-1-[4-methyl-3-(4-methyl-3-pyridyl)phenyl carbamoyl] indoline,
 1-[3-(pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-
 5 indoline,
 1-[3-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl-
 indoline,
 1-[3-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl
 indoline,
 10 1-[4-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl
 indoline,
 1-[4-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl
 indoline,
 1-[3-(3-pyridylcarbonyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 15 1-[3-(Pyrid-3-yl-aminosulphonyl)-phenylcarbamoyl]5-methoxy-6-trifluoromethyl-
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 5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-3-yloxy)pyridin-3-ylcarbomoyl]]indoline,
 20 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylmethyloxy)phenyl
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 5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-4-yl-methylamino carbonyl)phenyl
 25 carbamoyl]]indoline,
 Trans-5-Methylthio-6-trifluoromethyl-1-[4-[2-ethenyl-(4-pyridyl)]-phenyl
 carbamoyl]-indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-[2-ethyl(4-pyridyl)]phenyl carbamoyl]indoline,
 1-(1-(4-Pyridyl)-5-indolylcarbomoyl)-5-methoxy-6-trifluoromethylindoline,
 30 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylthiomethyl)phenyl
 carbamoyl]]indoline,
 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylsulphonylmethyl)
 phenylcarbomoyl]]indoline,
 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylmethylthio)phenyl
 35 carbamoyl]]indoline,
 5-Methylthio-6-trifluoromethyl-1-[(6-phenoxy)-3-pyridylcarbomoyl]-indoline,
 5-Methoxy-6-trifluoromethyl-1-[2-(pyridin-3-yloxy)pyridin-4-ylcarbomoyl]]indoline,

- 5-Methylthio-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[6-(6-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 5 5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-3-ylthio)pyridin-3-ylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-3-ylmethyl)amido phenyl carbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[3-(pyrid-4-ylmethyl)amidophenylcarbamoyl]indoline,
 10 5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-2-ylmethyl)amidophenylcarbamoyl]indoline,
 1-(1-(3-Pyridylmethyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
 1-(1-(4-Pyridylmethyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
 1-(1-(3-pyridyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline,
 15 5-Methylthio-6-trifluoromethyl-1-[3-[2-(3-pyridyl)thiazol-4-yl]phenylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-[2-(4-pyridyl)-thiazol-4-yl]phenyl carbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-[2-(3-pyridyl)-thiazol-4-yl]phenylcarbamoyl]indoline,
 20 1-[4-Fluoro-3-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[3-Fluoro-5-(pyrimidin-5-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[4-Chloro-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 25 1-[2,3-Dihydro-7-(pyrid-3-yl)benzofuran-5-ylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 5-Methoxy-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 30 5-Methoxy-6-trifluoromethyl-1-[6-(4-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 and pharmaceutically acceptable salts thereof.

Further preferred compounds are those of examples 83 - 177 and pharmaceutically acceptable salts thereof.

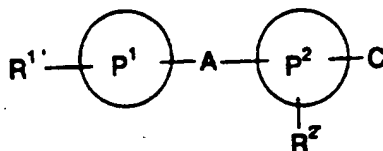
- 35 The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic. Preferred salts are mesylate salts.

Compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) the coupling of a compound of formula (II);



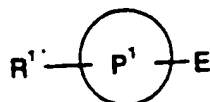
(II)

with a compound of formula (III);

D-R^{4'} (III)

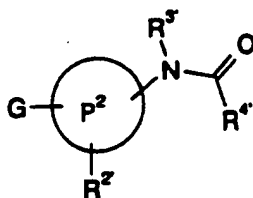
wherein A, P¹ and P² are as defined in formula (I), C and D contain the appropriate functional group(s) necessary to form the moiety -NR^{3'}CO when coupled, the variables R^{1'}, R^{2'}, R^{3'} and R^{4'} are R¹, R², R³ and R⁴ respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R^{1'}, R^{2'}, R^{3'} and R^{4'}, when other than R¹, R², R³ and R⁴ respectively to R¹, R², R³ and R⁴, interconverting R¹, R², R³ and R⁴ and forming a pharmaceutically acceptable salt thereof; or

(b) the coupling of a compound of formula (IV);



(IV)

with a compound of formula (V);



(V)

- 5 wherein P^1 , P^2 , R^1 , R^2 , R^3 and R^4 are as defined above and E and G contain the appropriate functional group(s) necessary to form the A moiety when coupled and thereafter optionally and as necessary and in any appropriate order, converting any R^1 , R^2 , R^3 and R^4 , when other than R^1 , R^2 , R^3 and R^4 respectively to R^1 , R^2 , R^3 and R^4 , interconverting R^1 , R^2 , R^3 and R^4 and forming a pharmaceutically acceptable salt.

Suitable examples of groups C and D include:

- (i) C is $-N=C=O$ and D is hydrogen,
- (ii) C is $-NR^{3'}COL$ and D is hydrogen,
- (iii) C is $-NHR^{3'}$ and D is COL, or
- 15 (iv) C is halogen and D is $-CONHR^{3'}$

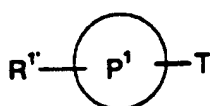
wherein $R^{3'}$ is as defined above and L is a leaving group. Examples of suitable leaving groups L include halogen such as chloro, bromo, imidazole, phenoxy or phenylthio optionally substituted, for example, with halogen.

- 20 Suitable examples of a group R^2 which are convertible to R^2 , include alkoxycarbonyl and benzyloxy or *para*-methoxybenzyloxy which are converted to the group where R^2 is hydroxy using conventional conditions.

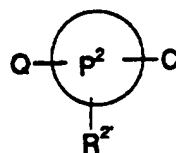
- Interconversions of R^1 , R^2 and R^3 are carried out by conventional procedures. For example R^1 halo can be introduced by selective halogenation of the ring P^1 using conventional conditions. It should be appreciated that it may be necessary to protect any R^1 to R^3 hydrogen variables which are not required to be interconverted.

Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

- 30 Compounds of formula (II) and (III) may be prepared according to known methods or analogous to known methods, for example using the procedures described in WO 95/01976. Compounds of formula (II) in which C is NH_2 , NO_2 or CO_2H can be prepared by reacting a compound of formula (VI) with a compound of formula (VII):



(VI)



(VII)

in which R^1 , R^2 , P^1 and P^2 are as defined in formula (II) and T and Q contain the appropriate functional groups necessary to form the A group. For example

- a) when A is a bond, one of T and Q is $\text{B}(\text{OH})_2$ or $\text{Sn}(\text{Bu})_3$ and the other is halogen or OTf (see for example Adv. Het. Chem. 1995, 62, 306).
- b) when A is a chain, one of T and Q is an acid chloride and the other is amino, or one of T and Q is hydroxy and the other is chloro or chloromethyl; or
- c) when A is a heterocyclic ring, one of T and Q is a thioamide group and the other is $\text{BrCH}_2\text{C}=\text{O}$.

Compounds of formula (III) may be prepared according to known methods or analogous to known methods, for example

- a) from the appropriate aniline via indole formation (Nordlander [JOC, 1981, 778] or Sundberg [JOC 1984, 249] routes) followed by reduction of the indole ring using sodium cyanoborohydride. It will be appreciated that in certain cases a mixture of indoles will be formed which can be separated at this stage or at a later stage.
- b) from the appropriate ortho-methyl nitrobenzene via indole formation (Leimgruber procedure Org Syn Coll vol VII, p34) followed by reduction of the indole ring.
- c) by aromatic substitution of a suitably protected indole/indoline precursor, for example alkylthio groups maybe introduced by thiocyanation of the indoline ring followed by hydrolysis and alkylation, or
- d) From the appropriate nitrobenzene via indole formation by aromatic nucleophilic substitution (J. Med. Chem. 1990, 2089) followed by reduction of the indole using NaCNBH_3 .

Novel intermediates of formula (III) also form part of the invention.

Suitable examples of reactions of compounds of formulae (IV) and (V) are those where E and G are the same as T and Q respectively in compounds of formulae (VI) and (VII) above. Compounds of formula (IV) are commercially available or can be prepared using standard procedures. Compounds of formula (V) can be prepared using standard procedures such as those outlined in WO 94/04533 or WO 95/01976.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have
5 5HT_{2B/2C} receptor antagonist activity and are believed to be of potential use for the treatment or prophylaxis of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also
10 disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides a compound of formula (I) or a
15 pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a
20 pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which
25 comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form
30 of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting
35 lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry

product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

5 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or
10 ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being
15 dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from
20 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit
25 doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable
30 toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1**6-Trifluoromethylindole line (D1)**

5 6-Trifluoromethylindole¹ (5.27g, 28.5 mmol) in glacial acetic acid (50 ml) was treated with sodium cyanoborohydride (3.60g, 57.0 mmol) portionwise at room temperature with stirring. After 3 h at room temperature the reaction mixture was diluted with water (100 ml) and basified with 40% aqueous NaOH with cooling. The mixture was then extracted with dichloromethane (3 x 150 ml) and the combined
10 extracts were dried (Na₂SO₄) and evaporated to give the title compound (4.83g, 91%) as a brown solid.

¹H NMR (CDCl₃) δ: 3.07 (2H, t, J = 8), 3.62 (2H, t, J = 8), 6.80 (1H, s), 6.92 (1H, d, J = 8), 7.15 (1H, d, J = 8).

1. A.N. Tischler and T.J. Lanza, *Tet. Lett.* 1986, 26, 1653.

15

Description 2**5-Thiocyanato-6-trifluoromethylindoline (D2)**

A mixture of 6-trifluoromethylindoline (D1) (9.7g, 52 mmol) and potassium
20 thiocyanate (10.09g, 104 mmol) in methanol (200 ml) was treated with a solution of bromine (2.82 ml, 55 mmol) in methanol (35 ml) dropwise over 0.5 h at -5-0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight then evaporated to dryness. The residue was partitioned between aqueous K₂CO₃ (100 ml) and dichloromethane (3 x 100 ml). The combined extracts were dried (Na₂SO₄)
25 and evaporated and the residue chromatographed on silica using 2-30% ethyl acetate/petroleum ether as eluant to afford the title compound (9.1g, 72%) as a yellow solid.

¹H NMR (CDCl₃) δ: 3.12 (2H, t, J = 8), 3.72 (3H, t, J = 8), 4.23 (1H, br s), 6.89 (1H, s), 7.50 (1H, s).

30

Description 3**Di[5-(6-trifluoromethylindoliny)]disulphide (D3)**

The thiocyanate (D2) (28.5g, 0.116 mol) in dioxane (200 ml) and water (100 ml) was
35 treated with aqueous ammonia (880, 200 ml) at 90° C for 1 h. The mixture was cooled and evaporated to give a residue which was partitioned between water (300 ml) and dichloromethane (4 x 300 ml). The combined extracts were dried (Na₂SO₄) and evaporated to give the title compound (25.5g, 100%) as a yellow solid.

^1H NMR(CDCl_3) δ : 3.03 (2H, t, $J = 8$), 3.67 (2H, t, $J = 8$), 4.00 (1H, br s), 6.80 (1H, s), 7.49 (1H, s).

5 Description 4

Di-[5-(1-acetyl-6-trifluoromethylindolyl)]disulphide (D4)

The disulphide (D3) (26g, 0.119 mol) in dichloromethane (300 ml) and triethylamine (47.3 ml, 0.339 mol) was treated dropwise with a solution of acetic anhydride (22.5 ml, 0.238 mol) in dichloromethane (50 ml) at 0°C . The mixture was allowed to warm to room temperature, stirred for 1 h then poured into 2.5 M aqueous HCl (400 ml). The organic layer was separated and the aqueous was further extracted with dichloromethane (200 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the title compound (29.1g, 94%) as a yellow solid.

^1H NMR (CDCl_3) δ : 2.22 (3H, s), 3.21 (2H, t), 4.10 (2H, t), 7.68 (1H, s), 8.47 (1H, s).

Description 5

1-Acetyl-5-mercapto-6-trifluoromethylindoline (D5)

20

A mixture of the diacetyl disulphide (D4) (28.5 g, 54.8 mmol), triphenylphosphine (20.85g, 79.5 mmol) and conc. aqueous HCl (1 ml) in dioxane (300 ml) and water (75 ml) was heated at reflux for 1.5 h. The reaction mixture was cooled and evaporated to a residue which was partitioned between dichloromethane (300 ml) and 1% aqueous NaOH (300 ml). The organic phase was further extracted with 1% aqueous NaOH (200 ml) and the combined aqueous fractions carefully acidified and extracted with dichloromethane (3 x 300 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the title compound (26g, 91%) as a yellow solid.

^1H NMR (CDCl_3) δ : 2.24 (3H, s), 3.20 (2H, t), 3.68 (1H, m), 4.11 (2H, t), 7.22 (1H, s), 8.51 (1H, s).

30

Description 6

1-Acetyl-5-methylthio-6-trifluoromethylindoline (D6)

35 A mixture of the thiol (D5) (26g, 99 mmol), anhydrous K_2CO_3 (15.12 g, 109 mmol) and iodomethane (18.6 ml, 300 mmol) in dry DMF (100 ml) was heated at 80°C for 1 h. The reaction mixture was cooled, evaporated *in vacuo* and partitioned between water (200 ml) and dichloromethane (3 x 200 ml). The combined organics were

washed with water (400 ml), dried (Na_2SO_4) and evaporated to yield the title compound (26.3g, 97%) as a yellow oil.

^1H NMR (CDCl_3) δ : 2.22 (3H, s), 2.49 (3H, s), 3.24 (2H, t, $J = 8$), 4.12 (2H, t, $J = 8$), 7.23 (1H, s), δ .51 (1H, s).

5

Description 7

5-Methylthio-6-trifluoromethylindoline (D7) Method (a)

10 The acetyl indoline (D6) (26.3g, 95 mmol) was treated with NaOH (30g, 750 ml) in water (150 ml) and ethanol (200 ml) at reflux for 1.5 h. The reaction mixture was cooled, diluted with water (200 ml) and most of the ethanol evaporated *in vacuo*. The remaining mixture was extracted with dichloromethane (3 x 200 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to afford the title compound (21.9g, 99%) as a yellow oil.

15 ^1H NMR (CDCl_3) δ : 2.41 (3H, s), 3.07 (2H, t), 3.63 (2H, t), 3.90 (1H, br s), 6.88 (1H, s), 7.30 (1H, s).

Method (b)

20 A stirred solution of potassium thiocyanate (38.6g, 0.39 mol) in methanol (470 ml) at -2°C under argon was treated dropwise over 10 minutes with bromine (10.3 ml, 0.195 mol) giving a yellow precipitate. The reaction mixture was stirred at 0°C for a further 15 minutes, then treated with a solution of 6-trifluoromethylindoline (D1) (33.2g, 0.177 mol) in methanol (320 ml) and allowed to warm to room temperature and stir for 4 h. A solution of potassium hydroxide (49.5g, 0.88 mol) in water (300 ml) was added in one portion, causing the temperature to rise to 43°C and a brown solution to be produced. The mixture was stirred at $43\text{--}45^\circ\text{C}$ for 25 minutes, then cooled to 12°C and treated with iodomethane (10.9 ml, 0.177 mol). The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h, then concentrated *in vacuo* to approx. 350 ml

30 volume. The residual aqueous mixture was extracted with dichloromethane (2 x 400ml) and the combined extract dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil (43 g), which was chromatographed on silica gel eluting with dichloromethane to afford the title compound (D7) as a light brown solid (25.3g, 61%) with spectral properties identical to those described above.

35

Description 8**1-Methoxy-4-nitro-2-trifluoromethylbenzene (D8)**

Sodium (11.78g, 0.512 mol) was dissolved in dry methanol (1 l) and to the resulting solution was added a solution of 1-chloro-4-nitro-2-trifluoromethylbenzene (96.22g, 0.427 mol) in methanol (100 ml). The reaction mixture was refluxed for 3 h then cooled and evaporated *in vacuo*. The residue was partitioned between water (500 ml) and dichloromethane (3 x 400 ml). The combined organic extracts were dried (Na₂SO₄) and evaporated to give the title compound (93.76g, 99%) as a white solid.

¹H NMR (CDCl₃) δ: 4.05 (3H, s), 7.12 (1H, d), 8.45 (1H, dd), 8.52 (1H, d).

Description 9**(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D9)**

A mixture of 1-methoxy-4-nitro-2-trifluoromethylbenzene (D8) (93g, 0.421 mol) and 4-chlorophenoxyacetonitrile (77.55g, 0.463 mol) in dry DMF (500 ml) was added dropwise over 0.75 h to a stirred solution of KO^tBu (103.85g, 0.927 mol) in dry DMF (400 ml) at -10° C. After complete addition the resulting purple solution was maintained at -10° C for 1 h then poured into a mixture of ice/water (1.5 l) and 5 M aqueous HCl (1.5 l). The resulting mixture was extracted with dichloromethane (3 x 1 l). The combined extracts were washed with water (3 l), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was chromatographed on silica using 10-40% ethyl acetate/petroleum ether as eluant to give the crude product which was recrystallised from ethyl acetate/petroleum ether to afford the title compound (85.13g, 78%) as a white solid. Mp 103-104 °C.

¹H NMR (CDCl₃) δ: 4.10 (3H, s), 4.37 (2H, s), 7.34 (1H, s), 8.53 (1H, s).

Description 10**5-Methoxy-6-trifluoromethylindole (D10)**

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D9) (85g, 0.327 mol) in ethanol/water (9:1, 1.6 l) and glacial acetic acid (16 ml) was hydrogenated over 10% palladium on carbon (50 g) at 50 psi for 0.5 h at room temperature. The reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between aqueous K₂CO₃ (1 l) and dichloromethane (2 x 1 l) and the combined organic extract was dried (Na₂SO₄) and evaporated to afford the title indole (67.63g, 96%) as a grey solid.

^1H NMR (CDCl_3) δ : 3.94 (3H, s), 6.53 (1H, m), 7.21 (1H, s), 7.32 (1H, m), 7.64 (1H, s), 8.25 (1H, br s).

Description 11

5 5-Methoxy-6-trifluoromethylindoline (D11)

The indole (D10) (67.63g, 0.315 mol) was treated with sodium cyanoborohydride (40 g, 0.637 mol) in glacial acetic acid (500 ml) as in the method of Description 1 to afford the title indoline (67.73g, 99%) as an off-white solid.

10 ^1H NMR (CDCl_3) δ : 3.07 (2H, t), 3.58 (2H, t), 3.67 (1H, br s), 3.83 (3H, s), 6.83 (1H, s), 6.88 (1H, s).

Description 12

15 3-(4-Pyridyl) aniline (D12)

3-Bromoaniline (0.24 ml, 2.2 mmol) and sodium carbonate (0.70g, 6.6 mmol) were suspended in a mixture of 1,2-dimethoxyethane (16 ml) and water (4 ml). The reaction mixture was then treated with 4-pyridyl boronic acid (0.27g, 2.2 mmol), and flushed with Argon. Tetrakis (triphenylphosphine)-palladium (0) (0.35g) was then added, and the mixture was heated to reflux under Argon for 24 hours. The reaction mixture was allowed to cool after which it was partitioned between dichloromethane and water. The aqueous layer was again extracted with dichloromethane. The combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow solid (0.35g). This was chromatographed on silica gel eluting with ethyl acetate to afford the title compound as a white solid (0.15g, 41%).

25 ^1H NMR (200 MHz, CDCl_3) δ (ppm): 8.63 (dm, 2H), 7.45 (dm, 2H), 7.35 (t, 1H), 7.0 (dm, 1H), 6.91(m, 1H), 6.75 (dm, 1H), 3.75 (b, 2H)

Description 13

30 3-(3-Pyridyl)aniline (D13)

A mixture of 3-bromopyridine (2.9ml, 4.74g, 30mmol), 3-aminophenyl boronic acid (4.63g, 30mmol), sodium carbonate (10g, 90mmol) and tetrakis (triphenylphosphine) palladium (0) (0.9g) in 1, 2-dimethoxyethane - water (150ml - 50ml) was heated to reflux under argon for 12h. The mixture was concentrated then partitioned between ethyl acetate/dilute brine. The organic extract was dried and evaporated affording a brown gum (6g). Chromatography on silica eluting with 50% ethyl acetate - 60/80

petroleum ether then ethyl acetate afforded the product as a yellow crystalline solid (4.8g, 95%).

¹H NMR (200MHz, CDCl₃) 3.8 (2H, 6s), 6.70 (1H, dm), 6.85 (1H, m), 6.95 (1H, m), 7.25 (1H, t), 7.35 (1H, m) 7.85 (1H, m), 8.60 (1H, dd), 8.85 (1H, d).

5

Description 14

1-(5-Bromo-pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethyl-indoline (D14)

10 A solution of 5-bromo-pyrid-3-yl acyl azide (3.16g, 13.9 mmol) in toluene (500ml) was heated to reflux under argon for 1h. The solution was allowed to cool to room temperature then added to a solution of 5-methoxy-6-trifluoro-methyl indoline (2.7g, 12.5mmol) in dichloromethane (200ml). The mixture was set aside in the fridge for 1h, then filtration and drying afforded the title compound as a white solid (4.62g, 89%), mp 220-222°C.

15 ¹H NMR (D⁶-DMSO) 3.30 (2H, t, J), 3.85 (3H, S), 4.20 (2H, t), 7.20 (1H, S), 8.10 (1H, S), 8.35 (2H, m), 8.75 (1H, S), 8.95 (1H, S).

Description 15

2-(3-Pyridyl)-thiazole-4-carbonyl azide (D15)

20

A suspension of 2-(3-pyridyl)-thiazole-4-carboxylic acid (0.824g, 4mmol) in dichloromethane-chloroform (30ml-15ml) was treated with triethylamine (0.75ml, 0.5g, 5mmol) and then iso-butyl chloroformate (0.65ml, 0.68g, 5mmol). After 1h the mixture was evaporated to dryness and the residue suspended in THF (30ml) and a solution of sodium azide (0.46g, 7mmol) in water (10ml) was added. After 1h, the mixture was concentrated (rotary evaporator) and partitioned between dichloromethane and brine. The organic extract was washed with half-saturated brine, dried, and evaporated. Trituration with petroleum ether, filtration, and drying in vacuo (CAUTION - no heating) afforded the title compounds as a brown solid

25

30 (0.37g, 40%).

Description 16

2-(2-Pyridyl)-thiophene-5-carbonyl azide (D16)

35 This was prepared in 45% yield by the same method as for Description 15.

Description 17**1-(3-Fluoro-5-iodophenylcarbamyl)-5-methoxy-6-trifluoromethylindoline (D17)**

- A mixture of 3-fluoro-5-iodoaniline (0.47g, 1.98 mmol) and 1,1'-carbonyl diimidazole (0.33g, 2 mmol) in dichloromethane (40 ml) was stirred at room temperature for 1 h, then evaporated to dryness. To the residue was added dimethylformamide (DMF, 10 ml) and a solution of 5-methoxy-6-trifluoromethylindoline (D11, 0.44g, 2 mmol) in DMF (5 ml). The mixture was heated at 80°C overnight, then cooled and poured into water. The precipitate was filtered off, washed with water and dried. The crude product was chromatographed on silica gel and eluted with dichloromethane. Eluted product was recrystallised from dichloromethane to give the title compound (0.38g, 40%), Mp. 221-4°C.
- $^1\text{H NMR}$ (d_6 DMSO) δ : 3.27 (2H, t, J=8), 3.84 (3H, s), 4.15 (2H, t, J=8), 7.20 (1H, s), 7.27 (1H, d, J=7), 7.57 (1H, d, J=12), 7.84 (1H, s), 8.10 (1H, s), 8.78 (1H, s).
- MS (EI) m/z = 480 (M^+), $C_{17}H_{13}N_2O_2F_4I$ requires $M=480$

Description 18**Ethyl 5-(2,6-difluorophenyl)nicotinate (D18)**

- A mixture of (2,6-difluorophenyl)tributyltin (1.18g, 2.9 mmol), ethyl 5-bromonicotinate (0.69g, 3 mmol) and tetrakis (triphenylphosphine) palladium (0) (0.10g) in xylene (10 mL) was heated under reflux for 24h, then cooled, filtered and evaporated. The residue was chromatographed on silica gel eluted with 20% ethyl acetate/petrol to give the title compound (0.64g, 84%).
- $^1\text{H NMR}$ (CDCl_3) δ : 1.43 (3H, t, J=7), 4.44 (2H, q, J=7), 7.06 (2H, t, J=7), 7.39 (1H, quintet, J=7), 8.42 (1H, s), 8.88 (1H, s), 9.23 (1H, s)
- MS (API): m/z =264 (MH^+), $C_{14}H_{11}NO_2F_2$ requires $M+1 = 264$

Description 19

- 5-(2,6-Difluorophenyl)nicotinoyl hydrazide (D19)**

- A mixture of ester (D18, 0.64g, 2.4 mmol) and 98% hydrazine hydrate (1 mL) in methanol (10 mL) was heated under reflux overnight, then cooled in ice. The precipitate was filtered off. The filtrate was evaporated and the residue was triturated with water before combining with the initial precipitate. The crude product was washed with ether and dried *in vacuo* to give the title compound (0.50g, 84%).
- $^1\text{H NMR}$ (d_6 DMSO) δ : 4.60 (2H, s), 7.29 (2H, t, J=7), 7.57 (1H, quintet, J=7), 8.28 (1H, s), 8.80 (1H, s), 9.03 (1H, s), 10.05 (1H, s).

MS (API): $m/z = 250$ (MH^+), $C_{12}H_9N_3OF_2$ requires $M+1 = 250$

Description 20

5-(2,6-Difluorophenyl)nicotinoyl azide (D20)

5

To a suspension of hydrazide (D19, 0.50g, 1.99 mmol) in concentrated hydrochloric acid (3 mL) and water (2 mL) at -5°C was added dropwise a solution of sodium nitrite (0.14g, 2.0 mmol) in water (2 mL). The mixture was stirred at -5°C for 0.5 h, then a solution of potassium carbonate (2.3g) in water (25 mL) was added cautiously.

10 The precipitate was filtered off, washed with water and dried *in vacuo* at room temperature to give the title compound (0.48g, 93%).

^1H NMR (CDCl_3) δ : 7.05 (2H, t, $J=7$), 7.40 (1H, quintet, $J=7$), 8.41 (1H, s), 8.93 (1H, s), 9.22 (1H, s)

MS (API) 261 (MH^+), 233 (MH^+-N_2)

15

Description 21

Phenyl N-(3-Bromo-5-(pyrid-3-yl)phenyl)carbamate (D21)

20 The title compound was prepared from 3-Bromo-5-(pyrid-3-yl)aniline using the method of Description 67.

^1H NMR 250MHz CDCl_3 δ : 7.1-7.9 (m, 9H), 8.6-8.7 (br, 1H, Ar), 8.8-8.9 (br, 1H, Ar)

Description 22

25 Phenyl N-[4-t-Butyl-3-(pyrid-3-yl)phenyl]carbamate (D22)

The title compound (0.18g, 68%) was prepared from 4-t-butyl-3-(pyrid-3-yl)aniline (0.175g, 0.00077 mole) using the method of Description 67.

^1H NMR (200 MHz, CDCl_3) δ : 1.18 (9H, s), 7.02-7.65 (11H, m), 8.49-8.62 (2H, m)

30

Description 23

Phenyl N-[4-Methoxy-3-(pyrid-3-yl)phenyl]carbamate (D23)

35 The title compound (0.48g, 75%) was prepared from 4-methoxy-3-(pyrid-3-yl)aniline (0.40g, 0.002 mole) using the method of Description 67.

^1H NMR (200 MHz, CDCl_3) δ : 3.80 (3H, s), 6.90-7.57 (10H, m), 7.88 (1H, dt), 8.56 (1H, dd), 8.78 (1H, d)

Description 24**Phenyl N-[5-Fluoro-4-methoxy-3-(pyrid-3-yl)phenyl]carbamate (D24)**

The title compound (0.48g, 79%) was prepared from 5-fluoro-4-methoxy-3-(pyrid-3-yl)aniline (0.40g, 0.0018 mole) using the method of Description 67.

¹H NMR (200 MHz, CDCl₃) δ: 3.75 (3H, s), 7.01-7.67 (8H, m), 7.82-8.08 (2H, m), 8.64 (1H, d), 8.80 (1H, s).

Description 25**1-(3,5-Dibromo-4-methylphenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline (D25)**

The title compound was prepared by the method of Example 1, from 3,5-dibromo-4-methylaniline (2.64g, 10 mmol), 1,1'-carbonyldiimidazole (1.64g, 10 mmol) and 5-methoxy-6-trifluoromethylindoline (D11) (2.2g, 10 mmol). Crude product was recrystallised from DMSO/water and washed with methanol and ether, to give the title compound (2.64g, 52%), mp >250°C.

NMR (d₆-DMSO) δ: 2.43 (3H, s), 3.26 (2H, t, J=8), 3.84 (3H, s), 4.14 (2H, t, J=8), 7.20 (1H, s), 7.96 (2H, s), 8.10 (1H, s), 8.72 (1H, s).

MS (API) 507 (MH⁺, ⁷⁹Br), 509 (MH⁺, ⁷⁹Br⁸¹Br), 511 (MH⁺, ⁸¹Br)

Description 26**1-[5-Bromo-(3-pyridylcarbamoyl)]-5-methoxy-6-trifluoromethyl indoline (D26)**

5-Bromo-3-pyridylcarbonylazide (3.7g, 16 mmoles) was heated under reflux in dry toluene (100 ml) for 1 hr. After cooling the resulting solution of isocyanate was treated with a solution of 5-methoxy-6-trifluoromethyl indoline (D11) (3.5g, 16 mmoles) in dichloromethane (600 ml) and stirred overnight. The mixture was concentrated *in vacuo* and the residue triturated with diethyl ether. Filtration and washing with more diethyl ether gave the title compound (D26) (5.4g, 81%).

¹H NMR (DMSO-d₆) δ: 3.30 (2H, t, J=8Hz), 3.83 (3H, s), 4.18 (2H, t, J=8Hz), 7.20 (1H, s), 8.10 (1H, s), 8.30-8.35 (1H, m), 8.71 (1H, s), 8.92 (1H, s)

Description 27**Phenyl N-[6-(Pyrid-3-yl)pyrid-3-yl]carbamate (D27)**

The title compound was prepared as in the method of description 67 from the corresponding aniline. This gave the title compound (0.66g, 100%)

M.S. (API) found m/z 292 (MH^+), $C_{17}H_{13}N_2O_2$ requires 292

Description 28

Phenyl-N-[3-(4-methylpyrid-3-yl)phenyl]carbamate (D28)

5

The title compound was prepared as in the method of description 67 from the corresponding aniline. This gave the title compound (0.8g, 100%)

NMR ($CDCl_3$) δ : 2.29 (3H, s), 7.10-7.40 (11H, m), 8.42-8.49 (2H, m)

10 **Description 29**

3-(5-Pyrimidyl)-aniline (D29)

This was prepared from 5-bromopyrimidine and 3-aminophenyl boronic acid in 84% yield by the same method as for Description 12.

15 1H NMR ($CDCl_3$) 3.80 (2H, bs), 6.80 (1H, dd), 6.90 (1H, m), 7.00 (1H, d), 7.30 (2H, m), 8.95 (2H, s), 9.20 (1H, s).

Description 30

Phenyl N-[3-ethyl-5-(pyrid-3-yl)phenyl]carbamate (D30)

20

The title compound (0.276g, 0.87 mmol) was prepared by the methodology of description 67, using 3-ethyl-5-(pyrid-3-yl)aniline, phenyl chloroformate (0.13ml, 0.96 mmol) and triethylamine (0.13ml, 0.96 mmol) in dichloromethane (10 ml)

25 1H NMR 250 MHz $CDCl_3$ δ : 8.78 (s, 1H, Ar), 8.51 (m, 1H, Ar), 7.08-7.92 (m, 5H, Ar), 2.51 (t, 2H, CH_2), 1.20 (q, 3H, Me)

Description 31

Phenyl N-[5-phenyl-3-(pyrid-3-yl)phenyl]carbamate

30 The title compound (0.289g, 100%) was prepared by methodology of description 67 using 5-phenyl-3-(pyrid-3-yl) aniline (0.194mg, 0.79 mmol), phenyl chloroformate (0.12 ml, 0.87 mmol) and triethylamine (0.12ml, 0.81 mmol) in DCM (10 ml)

1H NMR 250 MHz $CDCl_3$ δ : 8.92 (br, 1H, Ar), 8.65 (d, 1H, Ar), 7.95 (d, 1H, Ar), 7.82 (s, 1H, Ar), 7.72-7.12 (m, 8H, Ar)

35

Description 32**3-(3-Nitrobenzoylamino)-pyridine**

A solution of 3-aminopyridine (2 g, 20 mmol) in tetrahydrofuran (100 ml) was treated at 0° C with triethylamine (3 ml, 2.2 g, 22 mmol) and then a solution of 3-nitrobenzoyl chloride (3.7g, 20 mmol) in tetrahydrofuran (50 ml). After 0.5 h the reaction mixture was diluted with water (400 ml) and set aside in the fridge for 3 days. Filtration and drying afforded the title compound as a purple crystalline solid (4.82 g, 99%).

¹H NMR (D6-DMSO) 7.40 (1H, m), 7.85 (1H, t, J 8 Hz), 8.20 (1H, d, J 8 Hz), 8.30-8.50 (3H, m), 8.80 (1H, s), 8.95 (1H, d, J 2 Hz).

Description 33**3-(3-Aminobenzoylamino)-pyridine**

A solution of 3-(3-nitrobenzoylamino)-pyridine (2g, 8.23 mmol) in ethanol (200 ml) was treated with 10% palladium on charcoal (0.5 g) and hydrogenated at atmospheric pressure for 4 h. Filtration and evaporation afforded the product as a white solid (1.51g, 86%)

¹H NMR (D6-DMSO) 5.40 (2H, bs), 6.75 (1H, d, J 8 Hz), 7.0-7.2 (3H, m), 7.40 (1H, m), 8.15 (1H, d, J 8 Hz), 8.30 (1H, m), 8.90 (1H, d, J 2 Hz).

Description 34**5-Methylthio-6-trifluoromethyl-1-(3-ethoxycarbonyl phenyl carbamoyl)indoline**

To a stirred solution of carbonyl diimidazole (1.782g, 11 mmol) in dichloromethane (20 ml) was added dropwise a solution of ethyl 3-amino benzoate (1.65g, 10 mmol) in dichloromethane (20 ml). After 1 hour the reaction mixture was evaporated under reduced pressure before being treated with 5-methylthio-6-trifluoromethyl indoline (2.33g, 10 mmol) and dimethylformamide (30 ml) and heated to 100° C. After 1 hour the reaction mixture was cooled and water added forming a yellow precipitate. This was filtered and dried to give the product as a yellow solid (4.19g, 99%), m.p. 195-7° C.

¹H NMR (DMSO) δ: 8.85 (1H, s); 8.2 (2H, d, J6Hz); 7.9 (1H, d, J7Hz); 7.6 (1H, d, J7Hz); 7.4 (2H, t, J6Hz); 4.3 (2H, q, J7Hz); 4.2 (2H, t, J8Hz); 3.25 (2H, t, J8Hz); 2.5 (3H, s); 1.3 (3H, t, J7Hz).

Description 35**5-Methylthio-6-trifluoromethyl-1-(4-ethoxycarbonyl phenyl carbamoyl) indoline**

- This was made in the same manner as Description 34 using ethyl-4-amino benzoate to give the product as a yellow solid (3.948g, 93%), m.p. > 200° C.
- ¹H NMR (DMSO) δ: 8.95 (1H, s); 8.2 (1H, s); 7.9 (2H, d, J7Hz); 7.75 (2H, d, J7Hz); 7.4 (1H, s), 4.2 (4H, m); 3.25 (2H, t, J8Hz); 2.5 (3H, s); 1.3 (3H, t, J7Hz)

Description 36

- 5-Methylthio-6-trifluoromethyl-1-(3-carboxy phenyl carbamoyl)indoline**

- To a suspension of 5-methylthio-6-trifluoromethyl-1-(3-ethoxy carbonyl phenyl carbamoyl) indoline (3g, 7.1 mmol) in ethanol (30 ml) was added aqueous sodium hydroxide solution (5M) (7.1 ml, 35.5 mmol) and heated gently for 2 hours. It was then allowed to cool and acidified with aqueous hydrochloric acid (5M) forming a white precipitate which was filtered and dried to yield the product as a white solid (2.324g, 83%), mp >200° C.
- ¹H NMR (DMSO) δ: 12.95 (1H, s); 8.85 (1H, s); 8.2 (2H, s); 7.85 (1H, d, J7Hz); 7.6 (1H, d, J7Hz); 7.4 (2H, t, J7Hz); 4.2 (2H, t, J6Hz); 3.25 (2H, t, J6Hz); 2.5 (3H, s)

20

Description 37**5-Methylthio-6-trifluoromethyl-1-(4-carboxy phenyl carbamoyl) indoline**

- This was made in the same manner as Description 36 using 5-methylthio-6-trifluoromethyl-1-(4-ethoxycarbonyl phenyl carbamoyl) indoline to give the product as a pale green solid (2.455g, 88%), mp >200° C.
- ¹H NMR (DMSO) δ: 1.27 (1H, s); 8.9 (1H, s); 8.2 (1H, s); 7.9 (2H, d, J7Hz); 7.7 (2H, d, J7Hz); 7.4 (1H, s); 4.2 (2H, t, J8Hz); 3.75 (2H, t, J8Hz); 2.5 (3H, s)

- Description 38**

3-(Pyrid-3-ylaminosulphonyl)-nitrobenzene

- To a stirred solution of 3-aminopyridine (2g, 21.3 mmol) in pyridine (100 ml) was added 3-nitrobenzene sulphonyl chloride (4.43g, 20 mmol) and the mixture was heated to 50° C for 3 hours. After cooling it was partitioned between ethyl acetate and water and the organic washed with water (x2) and half saturated aqueous sodium chloride solution, separated, dried and evaporated to give a crude yield of 4.96g. It

was then triturated with dichloromethane and sonicated for 0.25 hours before being filtered and dried to give the product as a pink solid (4.279g, 72%)

¹H NMR (DMSO) δ: 10.9 (1H, s); 8.45 (2H, d, J7Hz); 8.3 (2H, s); 8.15 (1H, d, J7Hz); 7.9 (1H, t, J7Hz); 7.55 (1H, d, J7Hz); 7.3 (1H, q, J5Hz).

5

Description 39

3-(Pyrid-3-ylaminosulphonyl)-aminobenzene

To a solution of 3-(pyrid-3-ylaminosulphonyl)-nitrobenzene (4.279g, 15.3 mmol) in ethanol (500 ml)/dimethylformamide (50 ml) was added 10% palladium catalyst on charcoal (1g) and the reaction mixture was hydrogenated at atmospheric pressure for 2 hours. The reaction mixture was then filtered through kieselguhr before being evaporated under reduced pressure to give the product as a white solid (3.749g, 98%)

¹H NMR (DMSO) δ: 10.4 (1H, s); 8.25 (1H, s); 8.2 (1H, d, J5Hz); 7.5 (1H, d, J7Hz); 7.3 (1H, q, 5Hz); 7.15 (1H, t, J7Hz); 6.95 (1H, s); 6.8 (1H, d, J7Hz); 6.7 (1H, d, J7Hz); 5.6 (2H, s)

15

Description 40

3-(3-Nitrobenzoyl)pyridine

20

The title compound (1.55g, 25%) was prepared using the method of Langhals et al (Liebigs Ann. Chem. 1982, 930-949), and purified by flash column chromatography on silica gel, eluting with 30% ethyl acetate 60-80° petroleum ether

¹H NMR (200 MHz, CDCl₃) δ: 7.40-7.60 (1H, m); 7.75 (1H, t), 7.98-8.23 (2H, m), 8.50 (1H, dd), 8.59-8.70 (1H, m), 8.90 (1H, dd), 9.01 (1H, d)

25

Description 41

3-(3-Aminobenzoyl)pyridine

3-(3-Nitrobenzoyl)pyridine (1.55g, 0.006 mole) was suspended in ethanol (35 ml) and treated portionwise with a solution of tin (II) chloride (4.56, 0.024 mmole) in conc. HCl (7 ml). The reaction mixture was stirred at 50° C for 2 hours. After allowing to cool to room temperature, water (50 ml) was added and the mixture basified with 10% aqueous sodium hydroxide, extracted into ethyl acetate, dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound (1.14g, 85%) as a pale oil

¹H NMR (200 MHz; CDCl₃) δ: 3.90 (2H, s), 6.81-7.03 (1H, m), 7.03-7.20 (2H, m), 7.28 (1H, t), 7.39-7.59 (1H, m), 8.14 (1H, dd), 8.80 (1H, dd), 9.01 (1H, s)

35

Description 42**Trans-4-[2-ethenyl-(4-pyridyl)]-nitrobenzene (D42)**

A solution of (4-nitrobenzyl)triphenylphosphonium bromide (32g, 66 mmol in ethanol (100 ml) was treated with sodium methoxide (3.6g, 66 mmol). After 0.75 h
5 pyridine-4-carboxaldehyde (5.04 ml, 52.8 mmol) was added and the mixture stirred for 16 h. The mixture was subjected to an ethyl acetate/dilute brine workup. Drying, evaporation and chromatography afforded the product as an equal mixture of isomers. Recrystallisation from ethyl acetate petroleum ether afforded the title compound (single isomer) as a yellow solid (2.72g, 17%).

10 ¹H NMR (D6-DMSO) 7.50 (1H, d), 7.65 (2H, d), 7.70 (1H, d), 7.95 (2H, d), 8.30 (2H, d), 8.65 (2H, d).

Description 43**Trans-4-[2-ethenyl-(4-pyridyl)]-aniline (D43)**

A suspension of trans-4-[2-ethenyl-(4-pyridyl)]-nitrobenzene (D42) (0.5g, 2.2 mmol)
15 in ethanol (30 ml) at 50°C was treated with a solution of stannous (II) chloride (1.25g, 6.6 mmol) in concentrated hydrochloric acid (2 ml). The mixture was maintained at 50°C overnight then evaporated to dryness. The residue was partitioned between ethyl acetate and 5M aqueous sodium hydroxide solution. Drying and evaporation afforded a yellow solid which was triturated with ether-
20 petroleum ether (1:1) affording the title compound as a yellow solid (100 mg, 23%).

¹H NMR (D6-DMSO) 5.50 (2H, bs), 6.60 (2H, d), 6.85 (1H, d), 7.30-7.50 (5H, m), 8.45 (2H, d)

Description 44**4-Nitro-2-(pyridin-3-yloxy)pyridine-N-oxide (D44)**

25

Sodium hydride (0.27g of an 80% dispersion in oil, 9 mmol) was added to a solution of 3-hydroxypyridine (0.854g, 9 mmol) in THF (3 ml) at 0°C. The mixture was then stirred for 1 h at room temperature before 2-chloro-4-nitropyridine-N-oxide* (2g, 9 mmol) was added. The resulting solution was heated at reflux for 16h, cooled,
30 poured into water (100 ml) and extracted with dichloromethane (3 x 100 ml). The combined extracts were dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica using ethyl acetate as eluant to afford the title compound (1.74g, 83%) as a solid.

¹H NMR (250 MHz; CDCl₃) δ: 7.42 (2H, m), 7.83 (1H, m), 8.00 (1H, dd, J=8Hz, 2Hz), 8.42 (1H, d, J 8Hz), 8.51 (1H, m), 8.59 (1H, m).

* G.C. Finger and L.D. Starr, *J. Am. Chem. Soc.*, 81, 2674 (1959)

5 **Description 45**

4-Amino-2-(pyridin-3-yloxy)pyridine (D45)

4-Nitro-2-(pyridin-3-yloxy)pyridine-N-oxide (D44) (1g, 4.3 mmol) in acetic acid (75 ml) was treated with iron powder (1.2g, 21.4 mmol) at room temperature. After 2 h the mixture was concentrated under reduced pressure and partitioned between 2M aq NaOH (100 ml) and dichloromethane (4 x 100 ml). The combined extracts were dried and evaporated to a white crystalline solid (0.75g, 93%) which was used without further purification.

¹H NMR (250 MHz; CDCl₃) δ: 4.25 (2H, br), 6.17 (1H, d, J 2Hz), 6.33 (1H, dd, J 7Hz, 2Hz), 7.26 (1H, s), 7.32 (1H, dd, J 8Hz, 5Hz), 7.48 (1H, m, J 8Hz), 7.82 (1H, d, J 7Hz), 8.42 (1H, m, J 5Hz), 8.48 (1H, d, J 2Hz).

Description 46

5-Nitro-1-(3-pyridylmethyl)indole (D46)

5-Nitroindole (0.49, 3 mmol) was treated with sodium hydride (0.198g, 6.6 mmol) in dry dimethylformamide (20 ml). After 15 min at room temperature, 3-picolyl chloride hydrochloride (0.49g, 3 mmol) was added and the mixture was stirred at room temperature for 24 h, then poured into water. The precipitate was filtered off, washed with water and dried to give the title compound (0.67g, 88%), m.p. 131-4°C.

¹H NMR (CDCl₃) δ: 5.40 (2H, s), 6.75 (1H, d, J=3), 7.2-7.4 (4H, m), 8.09 (1H, dd, J=8,2), 8.52 (1H, s), 8.57 (1H, d, J=4), 8.61 (1H, d, J=2).

MS(API) m/z=254(MH⁺)

30 **Description 47**

5-Nitro-1-(4-pyridylmethyl)indole (D47)

The title compound was prepared by the method of Description 46 using 4-picolyl chloride hydrochloride. Yield 87%, m.p. 134-136°C

¹H NMR (CDCl₃) δ: 5.41 (2H, s), 6.80 (1H, d, J=3), 6.93 (2H, d, J=7), 7.23 (1H, d, J=8), 7.30 (1H, d, J=3), 8.10 (1H, dd, J=8,2), 8.57 (2H, d, J=7), 8.64 (1H, d, J=2)

MS(API) m/z=254(MH⁺)

Description 48**5-Amino-1-(3-pyridylmethyl)indole (D48)**

- To a stirred suspension of nitroindole (D46) (0.63g, 2.5 mmol), and iron powder
5 (0.41g, 7.2 mmol) in methanol (20 ml) was added a solution of ammonium chloride
(0.66g, 12.4 mmol) in water (13 ml). The mixture was then heated under reflux for
12 h, then filtered while hot and evaporated. The residue was diluted with water and
extracted with dichloromethane. The organic extract was washed with brine, dried
and evaporated to give the title compound (0.40g, 72%) as a gum.
10 ^1H NMR (CDCl_3) δ : 5.25 (2H, s), 6.38 (1H, d, $J=3$), 6.63 (1H, dd, $J=8,2$), 6.94 (1H,
d, $J=2$), 7.03 (1H, d, $J=8$), 7.05 (1H, d, $J=3$), 7.18 (1H, dd, $J=7,4$), 7.29 (1H, d, $J=7$),
8.52 (2H, broad s).
MS(API) $m/z=224(\text{MH}^+)$

15 Description 49**5-Amino-1-(4-pyridylmethyl)indole (D49)**

- The title compound was prepared by the method of Description 48, from nitroindole
D47. Yield 87%.
20 ^1H NMR (CDCl_3) δ : 3.52 (2H, broad), 5.27 (2H, s), 6.41 (1H, d, $J=3$), 6.63 (1H, dd,
 $J=8,2$), 6.90-7.0 (4H, m), 7.05 (1H, d, $J=3$), 8.50 (2H, d, $J=7$).
MS(API) $m/z=224(\text{MH}^+)$

Description 50**25 5-Nitro-1-(3-pyridyl)indole (D50)**

- A mixture of 5-nitroindole (0.49g, 3 mmol), 3-bromopyridine (0.95g, 6 mmol),
copper (I) bromide (60 mg, 0.42 mmol) and potassium carbonate (0.62g, 4.5 mmol)
in pyridine (2 mL) and nitrobenzene (0.6 mL) was heated under reflux for 4 h. After
30 cooling, the mixture was diluted with water and extracted with ethyl acetate. The
organic extract was washed with water, dried and evaporated. The residue was
chromatographed on silica gel eluted with ethyl acetate to give the title compound
(0.62g, 86.5%), mp. 164-5°C.
 ^1H NMR (CDCl_3) δ : 6.93 (1H, d, $J=3$), 7.49 (1H, d, $J=3$), 7.51 (1H, d, $J=8$), 7.57
35 (1H, dd, $J=7,5$), 7.87 (1H, dm, $J=7$), 8.18 (1H, dd, $J=8,2$), 8.72 (1H, d, $J=5$), 8.85
(1H, d, $J=2$)
MS(API) $m/z=240(\text{MH}^+)$

Description 51**5-Nitro-1-(4-pyridyl)indole (D51)**

- The title compound was prepared by the method of Description 50, using 4-bromopyridine. Yield 0.42g (59%)
- ¹H NMR (CDCl₃) δ: 7.09 (1H, d, J=3), 7.79 (2H, d, J=6), 7.94 (1H, d, J=8), 8.09 (1H, d, J=3), 8.13 (1H, dd, J=8,2), 8.69 (1H, d, J=2), 8.80 (2H, broad)
- MS(API) m/z=240(MH⁺)

10 Description 52**5-Amino-1-(3-pyridyl)indole (D52)**

- The title compound was prepared by the method of Description 48, from nitroindole (D50). Crude product was chromatographed on silica gel eluted with ethyl acetate to give the title compound (0.34g, 63%) as a gum.
- ¹H NMR (CDCl₃) δ: 3.59 (2H, broad), 6.55 (1H, d, J=3), 6.71 (1H, dd, J=8,2), 6.98 (1H, d, J=2), 7.25 (1H, d, J=3), 7.37 (1H, d, J=8), 7.64 (1H, dd, J=7,5), 7.82 (1H, dm, J=7), 8.58 (1H, d, J=5), 8.81 (1H, d, J=2)
- MS(API) m/z=210(MH⁺)

20

Description 53**5-Amino-1-(4-pyridyl)indole (D53)**

- A mixture of nitroindole (D51, 0.41g, 1.8 mmol), tin (II) chloride (1.7g, 8.8 mmol), and concentrated hydrochloric acid (2 ml) in ethanol (10 ml) was heated under reflux for 70 min. The mixture was evaporated and the residue was dissolved in water, basified with dilute sodium hydroxide and extracted with dichloromethane. The extract was dried and evaporated to give the title compound (0.36g, 96%).
- ¹H NMR (CDCl₃) δ: 3.62 (2H, broad), 6.56 (1H, d, J=3), 6.72 (1H, dd, J=8,2), 6.95 (1H, d, J=2), 7.32 (1H, d, J=3), 7.41 (2H, d, J=6), 7.54 (1H, d, J=8), 8.68 (2H, d, J=6)
- MS(API) m/z=210(MH⁺)

30

Description 54**5-Methylthio-6-trifluoromethyl-1-(3-ethoxycarbonylphenyl carbamoyl)-indoline (D54)**

- 5 This was prepared in 74% yield by urea formation between ethyl 3-aminobenzoate and 5-methylthio-6-trifluoromethyl indoline, (D7) using carbonyl diimidazole as the coupling agent.

Description 55

10 **5-Methylthio-6-trifluoromethyl-1-(3-carboxyphenylcarbamoyl)-indoline (D55)**

This was prepared in 86% by basic hydrolysis of the corresponding ester D54.

¹H NMR (CDCl₃) δ: 2.50 (3H, s), 3.30 (2H, t), 4.20 (2H, t), 7.40-7.50 (2H, m), 7.60 (1H, m), 7.85 (1H, d), 8.25 (2H, m), 8.80 (1H, s)

15

Description 56**4-(3-Nitrophenyl)-2-(3-pyridyl)-thiazole, hydrobromide salt**

- 20 A mixture of 2-bromo-3'-nitroacetophenone (5g, 20 mmol) and thionicotinamide (2.76g, 20 mmol) in ethanol (25 ml) was heated to reflux for 1 h, during which time extensive precipitation occurred. Filtration and drying afforded the product as a yellow solid (6.7g, 92%).

¹H NMR δ (DMSO) 7.80 (1H, t), 7.95 (1H, m), 8.25 (1H, dd), 8.55 (1H, d), 8.70 (1H, s), 8.90 (3H, m), 9.45 (1H, d)

25

Description 57**4-(3-Aminophenyl)-2-(3-pyridyl)-thiazole**

- 30 A suspension of 4-(3-nitrophenyl)-2-(3-pyridyl)-thiazole hydrobromide (3.6g, 10 mmol) in ethanol (150 ml) was treated with a solution of tin (II) chloride (3.7g, 30 mmol) in concentrated hydrochloric acid (12 ml). The mixture was heated at 50°C for 16 h. A further portion of tin (II) chloride (2.9 g, 15 mmol) was added and the mixture heated at 50°C for a further 4 hours before being evaporated to dryness. The residue was partitioned between ethyl acetate and 1M aqueous sodium hydroxide.

- 35 The ethyl acetate extract was dried (Na₂SO₄) and filtered through a plug of silica. Evaporation afforded the title compound as a yellow solid (2.15g, 85%).

¹H NMR (CDCl₃) δ: 3.80 (2H, bs), 6.70 (1H, dd), 7.20 (2H, m), 7.40 (2H, m), 7.50 (1H, s), 8.30 (1H, dt), 8.65 (1H, dd), 9.25 (1H, d).

Description 58**4-(4-Nitrophenyl)-2-(4-pyridyl)-thiazole**

This was prepared in the same manner as 4-(3-nitrophenyl)-2-(3-pyridyl)-thiazole, hydrobromide salt and liberated to the free base form with 5M NaOH to give the product as a brown solid (4g, 69%).

¹H NMR (CDCl₃) δ: 8.8 (2H, d), 8.35 (2H, d), 8.15 (2H, d), 7.9 (2H, d), 7.8 (1H, s).

Description 59**4-Fluoro-3-(pyrid-3-yl)phenylcarbonyl azide (D59)**

3-Bromo-4-fluorobenzotrifluoride was coupled with 3-pyridylboronic acid using Suzuki methodology. Hydrolysis of the product using conc. sulphuric acid and chlorosulphonic acid followed by esterification in methanol and conc. sulphuric acid gave methyl 4-fluoro-3-(pyrid-3-yl)benzoate. Treatment with hydrazine hydrate afforded the hydrazide which was diazotised with sodium nitrite and basified with potassium carbonate to give the title compound.

¹H NMR 250 MHz δ: 8.82 (br, 1H), 8.67 (br, 1H), 8.17 (dd, 1H), 8.09 (m, 1H), 7.90 (dd, 1H), 7.42 (m, 1H), 7.30 (m, 1H).

Description 60**3-Fluoro-5-(pyrimidin-5-yl)phenylcarbonyl azide (D60)**

3-Bromo-5-fluorobenzotrifluoride was lithiated with n-butyllithium and treated with tri-isopropylborate to give 3-fluoro-5-trifluoromethylphenyl boronic acid. This was coupled to 5-bromopyrimidine, using Suzuki methodology to afford 3-fluoro-5-(pyrimidin-5-yl)benzotrifluoride. Hydrolysis with conc. sulphuric acid and chlorosulphonic acid afforded 3-fluoro-5-(pyrimidin-5-yl)benzoic acid. This was converted to the methyl ester by treatment with methanol and conc. sulphuric acid, and to the hydrazide by treatment with hydrazine hydrate. Diazotisation and treatment with potassium carbonate afforded the title compound.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.57 (1H, dt J=1, 8), 7.83 (1H, m), 8.06 (1H, t, J=1), 8.99 (2H, s), 9.29 (1H, s)

Description 61**4-Chloro-3-(4-methyl-3-pyridyl)nitrobenzene (D61)**

The title compound was prepared by a Suzuki coupling of 3-bromo-4-chloronitrobenzene and 4-methyl-3-pyridylboronic acid. This gave (D61) (0.2g, 33%).

Description 62**4-Chloro-3-(4-methyl-3-pyridyl)aniline (D62)**

10

The title compound was prepared by stannous chloride reduction of the nitro compound (D61). This gave (D62) (0.105g, 95%).

Description 63**2,3-Dihydro-5-nitro-7-(pyrid-3-yl)benzofuran (D63)**

2,3-Dihydro-7-iodo-5-nitrobenzofuran (0.76g, 0.0026 mole) and 3-pyridylboronic acid (0.32g, 0.0026 mole) in 50% aqueous 1,2-dimethoxyethane (50 ml) were treated under argon with sodium carbonate (1.17g, 0.011 mole) and tetrakis triphenylphosphine palladium (0) (0.06g, 0.000052 mole) and heated under reflux for 18 hours. The mixture was allowed to cool to ambient temperature, diluted with deionised water, extracted into ethyl acetate, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 30% ethyl acetate/60-80° petroleum ether to afford the title compound (0.19g, 30%) as a yellow solid.

25

^1H NMR (200 MHz, CDCl_3) δ (ppm): 3.40 (2H, t, J=9), 4.83 (2H, t, J=9), 7.40 (1H, q, J=3, 5), 8.02 (1H, dt, J=1,9), 8.12 (1H, m), 8.30 (1H, d, J=3), 8.62 (1H, dd, J=1, 5), 8.98 (1H, d, J=1).

Description 64**5-Amino-2,3-dihydro-7-(pyrid-3-yl)benzofuran (D64)**

2,3-Dihydro-5-nitro-7-(pyrid-3-yl)benzofuran (D63) (0.19g, 0.00079 mole) in ethanol (20 ml) was treated with a solution of tin II chloride (0.75g, 0.0040 mole) in conc. hydrochloric acid (1 ml) and heated at 50°C for 2 hours. A further 0.38g tin II chloride in conc. hydrochloric acid (0.5 ml) was added and the mixture was heated at 50°C for ½ hour and stirred at ambient temperature for 18 hours. Deionised water (5 ml) was added and the mixture was basified with 10% sodium hydroxide solution,

35

extracted into ethyl acetate, dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound (0.13g, 82%) as a dark oil.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 3.20 (2H, t, $J=9$), 3.43-3.70 (2H, br s), 4.57 (2H, t, $J=9$), 6.63 (2H, s), 7.32 (1H, m), 8.01 (1H, dt, $J=1, 5$), 8.51 (1H, dd, $J=1, 5$),
5 8.89 (1H, t, $J=1$).

Description 65

Phenyl N-[2,3-dihydro-7-(pyrid-3-yl)benzofuran-5-yl]carbamate (D65)

10 5-Amino-2,3-dihydro-7-(pyrid-3-yl)benzofuran (D64) (0.13g, 0.00062 mole) was dissolved in dichloromethane (10 ml) and cooled to 0°C under argon. Triethylamine (0.09 ml, 0.00068 mole) was added, followed dropwise by phenyl chloroformate (0.08 ml, 0.00065 mole) and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was washed with deionised water, dried (Na_2SO_4) and
15 evaporated *in vacuo* to afford the title compound (0.20g, 97%) as a cream solid.
 ^1H NMR (200 MHz, CDCl_3) δ (ppm): 3.38 (2H, t, $J=9$), 4.64 (2H, t, $J=9$), 7.05-7.58 (9H, m), 8.06 (1H, dt, $J=1, 5$), 8.57 (1H, dd, $J=1, 5$), 8.95 (1H, d, $J=1$).

Description 66

20 Phenyl N-(3-Fluoro-5-(pyrid-3-yl)phenyl)carbamate (D66)

3-Fluoro-5-(pyrid-3-yl)aniline (1.05g, 0.0050 mole) in dry dichloromethane was treated under argon with triethylamine (1.12 ml, 0.0080 mole) followed dropwise by phenyl chloroformate (0.97 ml, 0.0077 mole) and stirred at ambient temperature for
25 18 hours. The reaction mixture was washed (x2) with deionised water, dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound (1.1g, 71%) as an off white solid.

^1H NMR (200 MHz; D_2O) δ : 7.20-7.49 (3H, m), 7.49-7.59 (5H, m), 7.63 (1H, d), 8.07 (1H, dt), 8.63 (1H, d), 8.87 (1H, s), 10.61 (1H, s)

30

Description 67

Phenyl N-(4-Chloro-3-(pyrid-3-yl)phenyl)carbamate (D67)

4-Chloro-3-(pyrid-3-yl)aniline (0.08g, 0.00039 mole) in isopropyl alcohol (8 ml) was cooled to -40°C and treated under argon with triethylamine (0.06 ml, 0.00043 mole) followed dropwise by phenyl chloroformate (0.051 ml, 0.00041 mole). The reaction mixture was stirred at -40°C for half an hour and allowed to warm to ambient temperature. The solvent was removed *in vacuo* and the residue dissolved in

35

dichloromethane, washed with H₂O, dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound (0.12g, 95%) as an orange solid.

¹H NMR (200 MHz; CDCl₃) δ: 7.05-7.56 (10H, m), 7.82 (1H, dt), 8.64 (1H, dd), 8.71 (1H, d)

5

Description 68

Phenyl N-[(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamate (D68)

The title compound (0.23g, 97%) was prepared using the method of D67.

10 ¹H NMR (200 MHz, CDCl₃) δ: 2.65 (3H, s), 7.08 (1H, s), 7.16-7.53 (6H, m), 7.66-7.87 (2H, m), 8.06 (1H, t).

Description 69

Phenyl N-[4-Methyl-3-(4-methylpyrid-3-yl)phenyl]carbamate (D69)

15

The title compound was prepared as in the method of description 67 from the corresponding aniline. This gave (2.1g, 97%) of an oil.

¹H NMR (CDCl₃) δ: 2.05 (3H, s), 2.15 (3H, s), 7.08-7.45 (10H, m), 8.30 (1H, s), 8.48 (1H, d, J=8Hz).

20

Example 1

1-[(3-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline

25 3-(3-Pyridyl)aniline (0.27g, 1.6mmol) in dichloromethane (5ml) was added dropwise over 5 minutes to a solution of 1,1-carbonyldiimidazole (0.28g, 1.75mmol) in dichloromethane (5ml). After 2 hour the mixture was evaporated to dryness and the residue dissolved in N,N-dimethylformamide (20ml). 5-Methoxy-6-trifluoromethyl indoline (0.35g, 1.6mmol) was added and the mixture heated to 100°C for 1h. Water (30ml) was added and the mixture was set aside in the fridge for 1h. Filtration and

30 drying afforded a brown solid (0.59g). Chromatography on silica, eluting with a gradient of 0-3% methanol in dichloromethane afforded the title compound as a white solid (0.56g, 85%), mp 193-4°C.

¹H NMR (D⁶ DMSO) 3.25 (2H, t), 3.85 (3H, s), 4.20 (2H, t) 7.20 (1H, s), 7.40 (2H, m), 7.50 (1H, m), 7.90 (1H, s), 8.05 (1H, dm), 8.15 (1H, s), 8.60 (1H, dm), 8.70 (1H, s), 8.85 (1H, s).

35

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

The following examples were similarly prepared:

Example 2**1-[(4-Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline**

5 Yield = 25%

¹H NMR (D⁶-DMSO) 2.52 (3H, s), 3.30 (2H, t), 4.25 (2H, t), 7.50 (3H, m), 7.70 (3H, m), 8.02 (1H, s), 8.25 (1H, s), 8.70 (2H, dd), 8.80 (1H, s).

Example 310 **1-[(3-Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline.**

Yield = 42%, m.p. 208-210°C

15 ¹H NMR (D⁶-DMSO) 2.50 (3H, s), 3.30 (2H, t), 4.20 (2H, t), 7.40 (3H, m), 7.50 (1H, m), 7.65 (1H, m), 7.90 (1H, s), 8.10 (1H, dm), 8.20 (1H, s), 8.60 (1H, m), 8.80 (1H, s), 8.90 (1H, m).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

Example 420 **1-[(3-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethylindoline.**

Yield = 85%, m.p. = >230°C

25 ¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.45 (1H, m), 7.70 (4H, m), 8.05 (1H, m), 8.15 (1H, s), 8.55 (1H, m), 8.70 (1H, s), 8.90 (1H, m)**Example 5****1-[(4-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline**

30 Yield = 5%, m.p. = >210°C

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.70 (2H, d), 7.75 (4H, m), 8.15 (1H, s), 8.60 (2H, d), 8.85 (1H, s)

Example 635 **1-[(2-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.**

Yield = 40%, m.p. = 220-225°C

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.40 (2H, m), 7.70 (2H, m), 7.90 (2H, m), 8.15 (1H, s), 8.35 (1H, s), 8.65 (1H, m), 8.70 (1H, s).

Example 7

5 **1-[4-Methyl-3-(3-Pyridyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline**

Yield = 26%, m.p. = 211-212°C

10 ¹H NMR (D⁶-DMSO) 2.2 (3H, s), 3.28 (2H, t), 3.85 (3H, s), 4.11 (2H, t), 6.44 (1H, s), 6.85 (1H, s), 7.18-7.45 (4H, m), 7.59-7.72 (1H, m), 8.22 (1H, s), 8.49-8.69 (2H, m).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

15 Example 8

1-[3-Fluoro-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline.

Yield = 26%, m.p. = 220-223°C

20 ¹H NMR (D⁶-DMSO) 3.29 (2H, t), 3.85 (3H, s), 4.21 (2H, t), 7.23 (1H, s), 7.30 (1H, t), 7.54 (2H, m), 7.65 (1H, dt), 7.76 (1H, s), 8.09 (1H, dt), 8.15 (1H, s), 8.62 (1H, dd), 8.78-9.00 (2H, m).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone. m.p. 198 - 199°C.

25

Example 9

1-[2-Fluoro-5-(3-pyridyl) phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

30

Yield = 10%, m.p. 233°C (decomp)

¹H NMR (D⁶-DMSO) 3.20 (2H, t), 3.82 (3H, s), 3.94 (2H, t), 7.13-7.28 (2H, m), 7.38-7.58 (3H, m), 7.87 (1H, dt), 7.98 (1H, s), 8.35 (1H, s), 8.55 (1H, dd), 8.64 (1H, d)

35

Example 10**1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethyl indoline**

A mixture of 1-(5-bromo-pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethyl-indoline (D14, 208mg, 0.5mmol), phenyl boronic acid (300mg, 2.4mmol), sodium carbonate (0.32g, 3mmol) and tetrakis (triphenylphosphine) palladium (0) (30mg) in dimethoxyethane-water (5ml-1ml) was heated to reflux under argon for 10h. The cooled reaction mixture was partitioned between ethyl acetate-half saturated brine. The organic extract was dried and evaporated affording a brown solid (0.14g).
10 Chromatography on silica, eluting with a gradient of 0-5% methanol in ethyl acetate afforded the title compound as a white crystalline solid (100mg, 48%), m.p. 162-164°C.

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (3H, t), 7.20 (1H, s), 7.50 (3H, m), 7.70 (2H, m), 8.10 (1H, s), 8.30 (1H, m), 8.55 (1H, m), 8.75 (1H, m), 8.85 (1H, s).
15 s).

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

The following examples were similarly prepared:

20 Example 11**1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methylthio-6-trifluoromethyl indoline**

Yield = 73%, m.p. = 208-214°C

¹H NMR (D⁶-DMSO) 2.50 (2H, s), 3.30 (2H, t), 4.20 (2H, t), 7.50 (4H, m), 7.70 (2H, m), 8.20 (1H, s), 8.30 (1H, m), 8.60 (1H, m), 8.75 (1H, m), 8.95 (1H, s).
25

Example 12**1-[5-(3-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.**

30 Yield = 29%, m.p. = 113-114°C

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.55 (1H, m), 8.10 (1H, m), 8.15 (1H, s), 8.30 (1H, m), 8.60 (1H,), 8.65 (1H, dd), 8.80 (1H, d), 8.95 (2H, m)

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.
35

Example 13

1-[5-(4-Trifluoromethylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline

- 5 Yield = 48%, m.p. = 199-202°C
 ¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.89 (4H, m), 8.10 (1H, s), 8.35 (1H, m), 8.60 (1H, d), 8.80 (1H, d), 8.95 (1H, s).

Example 14

- 10 **1-[5-(4-Methylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.**

- Yield = 57%, m.p. = 190-191°C
 ¹H NMR (D⁶-DMSO) 2.35 (3H, s), 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.30 (2H, d), 7.60 (2H, d), 8.15 (1H, s), 8.25 (1H, m), 8.55 (1H, d), 8.75 (1H, d),
15 8.85 (1H, s).

Example 15

- 20 **1-[5-(2-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline**

- Yield = 53%, m.p. = 193-208°C
 ¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (2H, m), 7.65 (2H, m), 8.10 (1H, s), 8.25 (1H, t), 8.60 (1H, d), 8.75 (1H, d), 8.90 (1H, s).
 The mesylate salt can be prepared by treatment with methanesulphonic acid in
25 acetone.

Example 16

- 1-[5-(3-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline**
- 30 Yield = 30%, m.p. = 165-167°C
 ¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.60 (1H, dd), 7.75 (1H, m), 8.0 (1H, m), 8.15 (1H, s), 8.30 (1H, t), 8.65 (1H, d), 8.70 (1H, d), 8.90 (1H, s)

Example 17

- 35 **1-[5-(2-Pyrrolyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.**

 Yield = 20%, m.p. = 218-219°C

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 6.20 (1H, m), 6.55 (1H, m), 6.90 (1H, m), 7.20 (1H, s), 8.15 (2H, m), 8.50 (1H, d), 8.60 (1H, d), 8.80 (1H, s).

5 Example 18

1-[5-(4-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline

Yield = 71%, m.pt 230-234°C.

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.75 (2H, m) 8.15 (1H, s), 8.40 (1H, t), 8.65 (1H, d), 8.70 (2H, m), 8.85 (1H, d).

Example 19

1-[2-(3-Pyridyl)-thiazol-4-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.

15 A solution of acyl azide (D15) (370mg, 1.6mmol) in toluene (5ml) was heated to reflux for 0.25h. After cooling to room temperature, the solution of the isocyanate was added to a solution of 5-methoxy-6-trifluoromethyl indoline (0.35g, 1.6mmol) in dichloromethane (10ml). Filtration and drying afforded the title compound as a white solid (100mg, 15%), m.p. >200°C.

20

¹H NMR 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.45 (1H, m), 7.55 (1H, s), 8.15 (1H, s), 8.30 (1H, dt), 8.65 (1H, dd), 9.15 (1H, m), 9.85 (1H, s).

Example 20

25 **1-[2-(2-Pyridyl)-thien-5-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline.**

This was prepared from the corresponding acyl azide (D16) using the same procedure as for Example 19, affording the title compound as a pale yellow solid (0.45g, 73%), m.p. 205-215°C.

30 ¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 6.80 (1H, d), 7.15 (1H, m), 7.25 (1H, s), 7.50 (1H, d), 7.75 (2H, m), 8.20 (1H, s), 8.45 (1H, m), 9.95 (1H, s).

Example 21

35 **1-(3-Fluoro-5-(4-methyl-3-pyridyl)phenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline**

A mixture of 1-(3-fluoro-5-iodophenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline (D17, 0.31g, 0.65 mmol), 4-methyl-3-pyridylboronic acid (88

- mg, 0.65 mmol), tetrakis (triphenylphosphine) palladium (O) (23 mg, 0.02 mmol) and sodium carbonate (0.31g, 3.0 mmol) in 1,2-dimethoxyethane (20 mL) and water (2 mL) was heated under reflux for 24 h, then cooled and poured into water. The aqueous mixture was extracted with dichloromethane/methanol, and the organic
- 5 extract was washed with brine, dried and evaporated. The residue was chromatographed on silica gel eluted with 2-3% methanol/dichloromethane to give the title compound, which was recrystallised from dichloromethane/petrol (80 mg, 28%), Mp 191-5°C.
- ¹H NMR (d₆DMSO) δ: 2.31 (3H, s), 3.28 (2H, t, J=8), 3.85 (3H, s), 4.19 (2H, t, J=8), 6.94 (1H, d, J=8), 7.22 (1H, s), 7.37 (1H, d, J=6), 7.42 (1H, s), 7.61 (1H, d, J=12), 8.12 (1H, s), 8.40 (1H, s), 8.46 (1H, d, J=6), 8.82 (1H, s)
- 10 MS (API): Found m/z=446 (MH⁺), C₂₂H₁₇N₃O₂F₄ requires M+1=446

Example 22

- 15 **1-(5-(2,6-Difluorophenyl)-3-pyridylcarbamoyl)-5-methoxy-6-trifluoromethylindoline**

- A solution of 5-(2,6-difluorophenyl)nicotinoyl azide (D20, 0.46g, 1.8 mmol) in toluene (10 mL) was heated under reflux for 2h. After cooling, a solution of 5-methoxy-6-trifluoromethylindoline (D11, 0.40g, 1.8 mmol) in dichloromethane (10
- 20 mL) was added and the mixture was stirred overnight at room temperature. The precipitate was filtered off and washed with petrol. The crude product was recrystallised from dichloromethane/petrol to give the title compound (0.66g, 82%), Mp. 217-9°C.
- 25 ¹H NMR (d₆DMSO) δ: 3.29 (2H, t, J=8), 3.84 (3H, s), 4.21 (2H, t, J=8), 7.22 (1H, s), 7.29 (2H, t, J=7), 7.56 (1H, quintet, J=7), 8.11 (1H, s), 8.15 (1H, s), 8.32 (1H, s), 8.80 (1H, s), 9.93 (1H, s).
- MS (API): m/z=450 (MH⁺), C₂₂H₁₆N₃O₂F₄ requires M+1 = 450
- Found: C, 54.84; H, 3.69; N, 8.64%
- 30 C₂₂H₁₆N₃O₂F₄ requires C, 58.80; H, 3.59; N, 9.35%

Example 23

6-Chloro-5-methyl-1-(4-methyl-3-(pyrid-3-yl)-phenylcarbamoyl) indoline

- 35 4-Methyl-3-(pyrid-3-yl) aniline (0.30g, 0.0016 mole) in dry dichloromethane (20 ml) was added, under argon, to 1,1'-carbonyldiimidazole in dry dichloromethane (10 ml) (0.30g, 0.0018 mole) and stirred at ambient temperature for 1 hour. The solvent was removed *in vacuo* and the residue dissolved in dry dimethylformamide (30 ml). 6-

Chloro-5-methylindole (see WO 95/01976) (0.27g, 0.0016 mole) in dry dimethylformamide (10 ml) was added and the mixture heated to 100°C for 1 hour.

After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue diluted with deionised water (15 ml), extracted into dichloromethane (2 x 20

5 ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 3% methanol/dichloromethane and the resulting solid recrystallised from ethyl acetate/methanol/60-80° petroleum ether to afford the title compound (0.31g, 57%) as a cream solid (mp 202-203°C).

¹H NMR (270 MHz, d⁶DMSO) δ: 2.20 (3H, s), 2.24 (3H, s), 3.12 (2H, t, J=7), 4.13
10 (2H, t, J=7), 7.14 (1H, s), 7.25 (1H, d, J=7), 7.42-7.61 (3H, m), 7.81 (1H, dt, J=3, 7), 7.89 (1H, s), 8.49-8.69 (3H, m)

MS (EI) m/z = 377 (M⁺)

The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

15

Example 24

1-(4-Methyl-3-(pyrid-3-yl) phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl indoline

20 4-Methyl-3-(pyrid-3-yl) aniline (0.35g, 0.0019 mole) in dry dichloromethane (20 ml) was added, under argon, to 1,1'-carbonyldiimidazole (0.34g, 0.0021 mole) in dry dichloromethane (10 ml) and stirred at ambient temperature for 1 hour. The solvent was removed *in vacuo* and the residue dissolved in dry dimethylformamide (10 ml).

25 5-Thiomethyl-6-trifluoromethylindoline (D7) (0.44g, 0.0019 mole) in dry dimethylformamide (5 ml) was added and the mixture heated to 100°C for 2 hours.

After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue diluted with deionised water (15 ml), extracted into dichloromethane (2 x 20 ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue purified by flash column chromatography on silica gel eluting with 3% methanol/ dichloromethane and the
30 resulting solid was recrystallised from ethyl acetate/60-80° petroleum ether to afford the title compound (0.11g, 13%) as a cream solid (mp 221-223°C)

¹H NMR (200 MHz; d⁶DMSO) δ: 2.20 (3H, s), 2.55 (3H, s), 3.38 (2H, t, J=8), 4.20 (2H, t, J=8), 7.26 (1H, d, J=9), 7.41-7.61 (4H, m), 7.81 (1H, dt, J=3,9), 8.20 (1H, s), 8.51-8.63 (2H, m), 8.69 (1H, s)

35 MS (CI) m/z=444 (MH⁺)

Example 25**1-(3-Fluoro-5-(pyrid-3-yl)phenylcarbamoyl)-5-thiomethyl-6-trifluoromethylindoline hydrochloride**

- 5 Phenyl N-(3-fluoro-5-(pyrid-3-yl)phenyl)carbamate (D66) (0.55g, 0.0018 mole) in dry dimethylformamide (30 ml) was treated, under argon, with 5-thiomethyl-6-trifluoromethyl indoline hydrochloride (D7) (0.49g, 0.0018 mole) and triethylamine (0.5 ml, 0.0036 mole) and heated to 100°C for 6 hours. After cooling to ambient temperature, the solvent was removed *in vacuo*. The residue was purified by flash
10 column chromatography on silica gel, eluting with 3% methanol/dichloromethane and the resulting solid recrystallised from ethyl acetate/60-80° petroleum ether to afford the title compound (0.39g, 49%) as an off white solid (mp 202-203°C)
¹H NMR (250 MHz, d⁶DMSO) δ: 2.52 (3H, s), 3.32 (2H, t, J=8), 4.22 (2H, t, J=8), 7.30 (1H, d, J=8), 7.45-7.58 (3H, m), 7.64 (1H, d, J=11), 7.78 (1H, s), 8.09 (1H, d, J=8),
15 8.23 (1H, s), 8.63 (1H, d, J=6), 8.87-9.01 (2H, m)
MS (Electron Spray) m/z=448 (MH⁺)

Example 26**1-(4-Chloro-3-(pyrid-3-yl)phenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline**
20

- Phenyl N-(4-Chloro-3-(pyrid-3-yl)phenyl)carbamate (D67) (0.12g, 0.00037 mole) in dry dimethylformamide (6 ml) was treated under argon, with 5-methoxy-6-trifluoromethylindoline (D11) (0.08g, 0.00037 mole) and heated to 120°C for 2
25 hours. After cooling to ambient temperature, the solvent was removed *in vacuo*. The residue was partitioned between 1N aqueous sodium hydroxide solution and dichloromethane. The organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The residue was triturated in diethyl ether, filtered and dried *in vacuo* at 60°C to afford the title compound (0.06g, 36%) as a grey-green solid (mp 210-213°C)
30 ¹H NMR (200 MHz; CDCl₃) δ: 3.30 (2H, t, J=9), 3.87 (3H, s), 4.12 (2H, t, J=9), 6.56 (1H, s), 6.87 (1H, s), 7.29-7.58 (4H, m), 7.81 (1H, d, J=8), 8.21 (1H, s), 8.60 (1H, d, J=5), 8.69 (1H, d, J=3).
MS (EI) m/z = 447 (M⁺)

Example 27**5-Methoxy-1-(5-methyl-(1,2,4-oxadiazol-3-yl)-phenylcarbamoyl)-6-trifluoromethyl indoline (E27)**

- 5 Phenyl N-(5-Methyl-(1,2,4-oxadiazol-3-yl)phenyl)carbamate (D68) (0.23g, 0.00078 mole) in dry dimethylformamide (10 ml) was treated, under argon, with 5-methoxy-6-trifluoromethylindoline (0.17g, 0.00078 mole) (D11) and heated to 120°C for 4 hours. After cooling to ambient temperature, the solvent was removed *in vacuo*. The residue was partitioned between water and dichloromethane and the organic layer was
- 10 dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with 5% methanol/dichloromethane. The resulting solid was recrystallised from ethyl acetate/60-80° petroleum ether to leave the title compound (0.11g, 34%) as a beige solid (mp 203-204°C)
- 15 ¹H NMR (250 MHz; d⁶DMSO) δ: 2.68 (3H, s), 3.30 (2H, t, J=8), 3.85 (3H, s), 4.21 (2H, t, J=8), 7.21 (1H, s), 7.49 (1H, t, J=7), 7.66 (1H, d, J=7), 7.81 (1H, d, J=7), 8.16 (1H, s), 8.33 (1H, s), 8.82 (1H, s)
- MS (Electron Spray) m/z = 419 (MH⁺)

Example 28

- 20 1-[4-Methyl-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline (E28)

- Phenyl N-(4-Methyl-3-(4-methylpyrid-3-yl)phenyl)carbamate (D69) (0.5g, 0.0016 mole) in dry dimethylformamide (20 ml) was treated with 5-methoxy-6-
- 25 trifluoromethylindoline (D11) (0.34g, 0.0016 mole) under argon and heated to 100°C for 6 hrs. The mixture was allowed to cool and evaporated to dryness *in vacuo*. The residue was dissolved in dichloromethane and the solution washed with 10% aqueous sodium hydroxide solution (2 x 20 ml) and then with saturated aqueous sodium chloride solution (30ml). The organic phase was then dried (Na₂SO₄) filtered and
- 30 evaporated to dryness. The residue was purified by flash chromatography on silica gel eluting with 1% methanol/dichloromethane. Trituration of the resulting residue with diethyl ether gave the title compound (E28) (0.326g, 47%) m.p. 138-140° C.
- ¹H NMR (CDCl₃) δ: 2.00 (3H, s), 2.13 (3H, s), 3.25 (2H, t, J=8Hz), 3.82 (3H, s), 4.12 (2H, t, J=8Hz), 6.62 (1H, s), 6.81 (1H, s), 7.11-7.29 (3H, m), 7.39-7.45 (1H, m),
- 35 8.20 (1H, s), 8.30 (1H, s), 8.44 (1H, d, J=6Hz)
- M.S. found 442 (MH⁺), C₂₄H₂₂N₂O₂F₃H⁺ requires 442

Example 29**1-[5-Bromo-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline (E29)**

- 5 The title compound was prepared from phenyl N-[3-bromo-5-(pyrid-3-yl)phenyl]carbamate (D21) and 5-methoxy-6-trifluoromethylindoline (D11) using the method of Example 28.

¹H NMR 250 MHz CDCl₃ δ: 8.74 (1H, s, Ar), 8.54 (dd, 1H, Ar), 8.19 (s, 1H, Ar), 7.88 (d, 1H, Ar), 7.74 (s, 1H, Ar), 7.6 (s, 1H, Ar), 7.32-7.44 (m, 2H, Ar), 6.82 (br s, 1H, Ar), 4.15 (t, 2H, indoline), 3.85 (s, 3H, Me), 3.25 (t, 2H, indoline)

Example 30**1-[4-t-Butyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline (E30)**

- 15 The title compound (0.055g, 23%) was prepared from phenyl N-[4-t-butyl-3-(pyrid-3-yl)phenyl]carbamate (D22) (0.18g, 0.00052 mole) and 5-methoxy-6-trifluoromethylindoline (D11) using the method of Example 28.

¹H NMR (200 MHz, CDCl₃) δ: 1.25 (9H, s), 3.27 (2H, t, J=11), 3.85 (3H, s), 4.09 (2H, t, J=11), 6.43 (1H, s), 6.85 (1H, s), 7.00 (1H, d, J=1), 7.18-7.35 (1H, m), 7.39-7.69 (3H, m), 8.20 (1H, s), 8.42-8.69 (2H, m)

MS (Electron Spray) m/z = 470 (MH⁺)

Example 31

- 25 **1-[4-Methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline (E31)**

The title compound (0.21g, 32%) was prepared from phenyl N-[4-methoxy-3-(pyrid-3-yl)phenyl]carbamate (D23) (0.48g, 0.0015 mole) and 5-methoxy-6-trifluoromethylindoline (D11) using the method of Example 28.

¹H NMR (200 MHz, D₂O) δ: 3.26 (2H, t, J=9), 3.76 (3H, s), 3.83 (3H, s), 4.14 (2H, t, J=9), 7.10 (1H, d, J=7), 7.19 (1H, s), 7.45 (1H, dd, J=1,5), 7.54 (1H, s), 7.59 (1H, d, J=3), 7.87 (1H, dt, J=1,5), 8.10 (1H, s), 8.47-8.55 (2H, m), 8.67 (1H, d, J=3).

MS (Electron Spray) m/z=444 (MH⁺)

- 35 The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

Example 32**1-[5-Fluoro-4-methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline (E32)**

- 5 The title compound (0.34g, 53%) was prepared from phenyl N-[5-fluoro-4-methoxy-3-(pyrid-3-yl)phenyl]carbamate (D24) (0.48g, 0.0014 mole) and 5-methoxy-6-trifluoromethylindoline (D11) using the method of Example 28.

¹H NMR (200 MHz, D²O) δ: 3.38 (2H, t, J=8), 3.68 (3H, s), 3.84 (3H, s), 4.17 (2H, t, J=8), 7.21 (1H, s), 7.43 (1H, s), 7.51 (1H, dd, J=5, 9), 7.66 (1H, dd, J=3, 20),
 10 7.91 (1H, dt, J=1,8), 8.12 (1H, s), 8.61 (1H, dd, J=3,5), 8.70 (1H, d, J=3), 8.75 (1H, s).

MS (Electron Spray) m/z=462 (MH⁺)

Example 33

- 15 **1-[3-Bromo-4-methyl-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline (E33)**

A mixture of 1-(3,5-dibromo-4-methylphenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline (D25, 0.51g, 1 mmol), 3-pyridylboronic acid (0.12g, 1
 20 mmol), tetrakis (triphenylphosphine)palladium (0) (35 mg, 0.03 mmol) and sodium carbonate (0.41g, 4 mmol) in dimethoxyethane (30 mL) and water (3 mL) was heated under reflux, under argon, for 18 h. The mixture was cooled and poured into water. The precipitate was filtered off, washed with water and dried. The crude product was chromatographed on silica gel, eluted with ethyl acetate, and the eluted material was
 25 triturated with ether to give the title compound (0.14g, 28%), m.p. 216-8°C.

NMR (d₆-DMSO) δ: 2.20 (3H, s), 3.25 (2H, t, J=8), 3.84 (3H, s), 4.15 (2H, t, J=8), 7.20 (1H, s), 7.50 (1H, s + 1H, m), 7.82 (1H, d, J=7), 8.03 (1H, s), 8.11 (1H, s), 8.57 (1H, s), 8.62 (1H, d, J=4), 8.71 (1H, s).

MS (API) m/z 506 (MH⁺, ⁷⁹Br), 508 (MH⁺, ⁸¹Br)

30

Example 34**1-[3-(4-Isoquinolyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline**

- The title compound was prepared by the method of Example 23, from 4-(3-
 35 aminophenyl)isoquinoline (0.41g, 1.9 mmol), 1,1'-carbonyldiimidazole (0.33g, 2 mmol) and 5-methoxy-6-trifluoromethylindoline (D11) (0.41g, 1.9 mmol). Crude product was chromatographed on silica gel eluted with 5% methanol/dichloromethane

and eluted material was recrystallised from dichloromethane to give the title compound (0.22g, 25%), m.p. 211-5°C.

NMR (d_6 -DMSO) δ : 3.28 (2H, t, J=8), 3.85 (3H, s), 4.21 (2H, t, J=8), 7.20 (1H, d, J=7), 7.22 (1H, s), 7.50 (1H, t, J=8), 7.76 (2H, m), 7.78 (1H, s), 7.82 (1H, t, J=7),
 5 7.93 (1H, d, J=8), 8.1 (1H, s), 8.25 (1H, d, J=8), 8.47 (1H, s), 8.73 (1H, s), 9.38 (1H, s)

Found: C, 67.01; H, 4.51; N, 9.03%

$C_{22}H_{20}N_4O_2F$, requires C, 67.38; H, 4.35; N, 9.07%

MS (API) 464 (MH^+)

10 The mesylate salt can be prepared by treatment with methanesulphonic acid in acetone.

Example 35

15 1-[5-(4-Methyl-3-pyridyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethylindoline (E35)

1-[5-Bromo-(3-pyridylcarbamoyl)]-5-methoxy-6-trifluoromethylindoline (D26) (0.3g, 0.7 mmol) and 4-methyl-3-pyridylboronic acid (0.12g, 0.9 mmol) was heated under reflux in dimethoxyethane (80 ml) and water (10 ml) with sodium carbonate (0.15g, 1.4 mmol) and palladium tetrakis triphenylphosphine (0.1g, 12 mole %)
 20 under an inert atmosphere for 18 hours. After cooling the mixture was partitioned between ethyl acetate (250 ml) and water (200 ml). The organic layer was separated and washed with saturated sodium chloride solution then dried (Na_2SO_4).

Evaporation of the solvent followed by flash chromatography on silica gel eluting with 3-7% MeOH/ CH_2Cl_2 and recrystallisation from ethyl acetate/60-80 petrol gave the title compound (E35) (0.2g, 65%) m.p. 125-8°C.

1H NMR ($CDCl_3$) δ : 2.32 (3H, s), 3.32 (2H, t, J=8Hz), 3.85 (3H, s), 4.18 (2H, t, J=8Hz), 6.90 (2H, s), 7.21 (1H, d, J=4Hz), 8.10 (1H, s), 8.18 (1H, s), 8.27 (1H, s), 8.40 (1H, s), 8.45-8.53 (2H, m).

30 M.S. found m/z 429 (MH^+) $C_{22}H_{17}N_4O_2F$, requires 429.

Example 36

1-[6-(3-Pyridyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethylindoline

35 Reaction of Phenyl N-[6-(pyrid-3-yl)pyrid-3-yl]carbamate (D27) (0.66g, 2.3 mmol) with 5-methoxy-6-trifluoromethylindoline (D11) (0.5g, 2.3 mmol) as in the method of example 28 gave the title compound (E36) (0.73g, 78%) m.p. >270°C.

¹H NMR (DMSO-d⁶) δ: 3.32 (2H, t, J=8Hz), 3.88 (3H, s), 4.23 (2H, t, J=8Hz), 7.20 (1H, s), 7.45-7.55 (1H, m), 7.98-8.18 (3H, m), 8.35-8.43 (1H, m), 8.55-8.60 (1H, m), 8.85 (1H, d, J=4Hz), 8.91 (1H, s), 9.23 (1H, s).

MS (API) found m/z 415 (MH⁺) C₂₁H₁₇N₄O₂F₃ requires 415

5

Example 37

1-[5-(2-Furyl)-pyrid-3-ylcarbamoyl-5-methoxy-6-trifluoromethyl indoline (E37)

10 This was prepared from 1-(5-bromopyrid-3-ylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline and 2-furylboronic acid by the same method as for Example 10, affording the title compound as a pale brown crystalline solid in 80% yield, m.p. 92-94°C.

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 6.65 (1H, m), 7.10 (1H, d), 7.25 (1H, s), 7.85 (1H, s), 8.15 (1H, s), 8.30 (1H, t), 8.60 (1H, d), 8.65 (1H, d),
15 8.90 (1H, bs).

Example 38

1-[2-(4-Pyridyl)-thiazol-4-ylcarbamoyl-5-methoxy-6-trifluoromethyl indoline

20 This was prepared from 2-(4-pyridyl)-thiazole-4-carboxylic acid by the same methodology as for Description 15 and Example 19, affording the title compound as a yellow crystalline solid in 8% overall yield, m.p. >220°C.

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.75 (1H, s), 7.90 (2H, d), 8.15 (1H, s), 8.70 (2H, d), 9.90 (1H, bs).

25

Example 39

1-[2-(Pyrazinyl)-thiazol-4-ylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline

30 This was prepared from 2-pyrazinyl-thiazole-4-carboxylic acid by the same methodology as for Description 15 and Example 19, affording the title compound as a yellow crystalline solid in 45% overall yield, m.p. >240°C.

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.75 (1H, s), 8.20 (1H, s), 8.75 (2H, m), 9.30 (1H, s), 9.90 (1H, s)

Example 40**1-[3-(5-Pyrimidyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline**

5 This was prepared from 3-(5-pyrimidyl)-aniline (D29) and 5-methoxy-6-trifluoromethyl-indoline (D11), according to the method of Example 1, affording the title compound in 69% yield as a white crystalline solid, m.p. 226-8°C.

¹H NMR (D⁶-DMSO) 3.30 (2H, t), 3.85 (3H, s), 4.20 (2H, t), 7.20 (1H, s), 7.45 (2H, m), 7.70 (1H, m), 7.95 (1H, s), 8.15 (1H, s), 8.70 (1H, s), 9.10 (2H, s), 9.20 (1H, s)

10 Example 41**1-[3-(4-Methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline**

15 Reaction of phenyl-N-[3-(4-methylpyrid-3-yl)phenyl]carbamate (D28) (0.4g, 1.3 mmoles) with 5-methoxy-6-trifluoromethylindoline (D11) (0.28g, 1.3 mmoles) as in the method of Example 28 gave the title compound (E41) (0.19g, 34%) m.p. 178-180°C.

¹H NMR (DMSO-d⁶) δ: 2.29 (3H, s), 3.29 (2H, t, J=8Hz), 3.84 (3H, s), 4.19 (2H, t, J=8Hz), 7.01 (1H, d, J=6Hz), 7.20 (1H, s), 7.31-7.43 (2H, m), 7.55-7.62 (2H, m),
20 8.10 (1H, s), 8.32 (1H, s), 8.40 (1H, d, J=6Hz), 8.62 (1H, s).

M.S. (API) found m/z 428 (MH⁺) C₂₂H₂₂N₃O₂F, requires 428

Example 42**1-[5-Ethyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline**

25

The title compound (0.15g, 40%) was prepared as a tan powder using the methodology of Example 28 from phenyl N-(3-ethyl-5-(pyrid-3-yl)phenyl carbamate (D30) (0.26g, 0.81 mmol) and 5-methoxy-6-trifluoromethyl indoline (D11) (0.177g, 0.81 mmol) in DMF (10 ml). Melting point: 205°C-207°C

30 ¹H NMR 250 MHz, CDCl₃ δ: 8.81 (s, 1H, Ar), 8.58 (d, 1H, Ar), 8.22 (s, 1H, Ar), 7.88 (m, 1H, Ar), 7.48 (s, 1H, Ar), 7.32 (m, 2H, Ar), 7.12 (s, 1H, Ar), 6.85 (s, 1H, Ar), 6.52 (s, 1H, NH), 4.12 (t, 2H, indoline), 3.88 (s, 3H, Me), 3.28 (t, 2H, indoline), 2.60 (q, 2H, CH₂), 1.3 (t, 3H, Me).

Mass spec. m/z = 442 [M⁺1]⁺

35

Example 43**5-Methoxy-1-[5-phenyl-3-(pyrid-3-yl)phenylcarbamoyl]-6-trifluoromethyl indoline (E43)**

- 5 The title compound (0.74g, 47%) was prepared as an off white solid using the methodology of example 28, with phenyl N-(5-phenyl-3-(pyrid-3-yl)phenyl)carbamate (D31) (0.27g, 0.76 mmol) and 5-methoxy-6-trifluoromethyl indoline (D11) [0.182 mg, 0.83 mmol] in DMF (10 ml). Melting point: 150°-151°C
- 10 ¹H NMR 250 MHz CDCl₃ δ: 8.87 (s, 1H, Ar), 8.60 (d, 1H, Ar), 8.24 (s, 1H, Ar), 7.90 (m, 1H, Ar), 7.70-7.55 (m, 4H, Ar), 7.50-7.30 (m, 5H, Ar), 6.85 (br, 1H, Ar), 6.65 (br, 1H, NH), 4.12 (t, 2H, indoline), 3.85 (3H, s, Me), 3.28 (t, 2H, indoline)

Example 44

- 15 **6-Chloro-5-methyl-1-[4-methyl-3-(4-methyl-3-pyridyl)phenyl carbamoyl] indoline**

- Reaction of phenyl N-[4-methyl-3-(4-methylpyrid-3-yl)phenyl]carbamate (D69) (0.5g, 1.6 mmoles) with 6-chloro-5-methylindoline (see WO 95/01976) (0.26g, 1.6 mmoles) as in the method of Example 28 gave the title compound (E44) (0.23g, 38%) m.p.
- 20 178-180°C.
- ¹H NMR (CDCl₃) δ: 2.01 (3H, s), 2.12 (3H, s), 2.29 (3H, s), 3.15 (2H, t, J=8Hz), 4.07 (2H, t, J=8Hz), 6.60 (1H, s), 6.95 (1H, s), 7.15-7.28 (3H, m), 7.38-7.43 (1H, m), 7.95 (1H, s), 8.30 (1H, s), 8.42 (1H, s)
- MS (API) found m/z 392 (MH⁺, ³⁵Cl), 394 (MH⁺, ³⁷Cl)
- 25 C₂₀H₂₂N₂OCl requires 392, 394

Example 45

- 30 **1-[3-(pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline**

- A mixture of 3-(3-aminobenzoylamino)pyridine (D33) (0.416g, 2 mmol) and carbonyl diimidazole (0.34g, 2 mmol) in dichloromethane/N,N-dimethylformamide (25 ml/0.25 ml) was heated to reflux for 0.25 h, then evaporated to dryness. The residue was dissolved in N,N-dimethylformamide (15 ml) and 5-methoxy-6-
- 35 trifluoromethyl indoline (0.416 g, 2 mmol) was added. The mixture was heated to 100° C for 1 h then treated with water (30 ml). Filtration and drying afforded a white solid (0.5 g). Chromatography on silica eluting with a gradient of 0-20% methanol in

ethyl acetate afforded the title compound as a white solid (0.17g, 19%), m.p. >220° C.

- 5 ¹H NMR (D6-DMSO) 3.25 (2H, t, J 8 Hz), 3.85 (3H, s), 4.20 (2H, t, J 8 Hz), 7.25 (1H, s), 7.40-7.55 (2H, m), 7.65 (2H, d, J 8 Hz), 7.90 (1H, d, J 8 Hz), 8.10-8.30 (3H, m), 8.40 (1H, d, J 2 Hz), 8.10-8.30 (3H, m), 8.40 (1H, d, J 2 Hz), 8.85 (1H, s), 8.90 (1H, d, J 2 Hz), 10.50 (1H, s).
m/e 457 [MH]⁺ C₂₃H₁₉N₄F₃O₃ requires 457

Example 46

- 10 **1-[3-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl-indoline**

- 15 To a suspension of 5-methylthio-6-trifluoromethyl-1-(3-carboxy phenyl carbamoyl)indoline (D36) (0.5g, 1.25 mmol) in dichloromethane was added oxalyl chloride (0.324g, 2.5 mmol) and dimethylformamide (3 drops). After effervescence had subsided the reaction mixture was evaporated under reduced pressure before being dissolved in tetrahydrofuran (10 ml) and added dropwise to a solution of 3-aminopyridine (0.133 mg, 1.4 mmol) and triethylamine (0.141g, 1.4 mmol) in tetrahydrofuran (10 ml) at 0° C.
- 20 After 1 hour water was added forming a white precipitate which was filtered and dried to yield the product as a white solid (0.435g, 73%), mp 195-7° C.
¹H NMR (DMSO) δ: 10.5 (1H, s); 9.0 (2H, d, J5Hz); 8.4 (1H, d, J5Hz); 8. (1H, s); 8.25 (1H, s); 8.2 (1H, s); 7.9 (1H, d, J7Hz); 7.7 (1H, d, J7Hz); 7.5 (3H, m); 4.3 (2H, t, J8Hz); 3.3 (2H, t, J8Hz); 2.5 (3H, s)

25

Example 47

- 1-[3-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline**

- 30 This was made in the same manner as Example 46 using a solution of 4-aminopyridine to give the product as a peach solid (0.45g, 76%), mp >200° C.
¹H NMR (DMSO) δ: 10.7 (1H, s); 8.95 (1H, s); 8.5 (2H, d, J7Hz); 8.2 (1H, s); 8.1 (1H, s); 7.85 (1H, d, J7Hz); 7.8 (2H, d, J7Hz); 7.65 (1H, d, J7Hz); 7.45 (2H, m); 4.25 (2H, t, J7Hz); 3.3 (2H, t, J7Hz); 2.5 (3H, s)
- 35 m/e = 472 C₂₃H₁₉F₃N₄O₂S requires 472

Example 48

1-[4-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline

- 5 This was made in the same manner as Example 46 using 5-methylthio-6-trifluoromethyl-1-(4-carboxy phenyl carbamoyl) indoline (D37) to give the product as a pale yellow solid (0.327g, 55%), mp >200 °C.
- ¹H NMR (DMSO) δ: 10.6 (1H, s); 9.1 (1H, s); 9.0 (1H, s); 8.4 (2H, d, J7Hz); 8.2 (1H, s); 8.0 (2H, d, J7Hz); 7.8 (2H, d, J7Hz); 7.6 (1H, q, J5Hz); 7.4 (1H, s); 4.25 (2H t, J7Hz); 3.3 (2H, t, J7Hz); 2.5 (3H, s).
- 10 m/e = 472 C₂₃H₁₉F₃N₄O₂S requires 472

Example 49

- 1-[4-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline**
- 15

- This was made in the same manner as Example 48 using a solution of 4-aminopyridine to give the product as an orange solid (0.352g, 59%), mp 158-160° C.
- ¹H NMR (DMSO) δ: 10.5 (1H, s); 8.95 (1H, s); 8.5 (2H, d, J5Hz); 8.2 (1H, s); 7.9 (2H, d, J7Hz); 7.85 (2H, d, J5Hz); 7.8 (2H, d, J7z); 7.5 (1H, s); 4.25 (2H, t, J7Hz); 3.3 (2H, t, J7Hz); 2.5 (3H, s).
- 20 m/e = 472 C₂₃H₁₉F₃N₄O₂S requires 472

Example 50

- 1-[3-(3-pyridylcarbonyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline**
- 25

- The title compound (0.17g, 26%) was prepared using the method of Example 45, and purified by flash column chromatography on silica gel, eluting with 2% methanol/dichloromethane, and recrystallisation from ethylacetate/methanol/60-80° petroleum ether.
- 30 ¹H NMR (200 MHz; D⁶DMSO) δ: 3.28 (2H, t), 3.75 (3H, s), 4.20 (2H, t), 7.22 (1H, s), 7.38-7.49 (1H, m), 7.52 (1H, t), 7.63 (1H, q), 7.93-8.00 (1H, m), 8.02 (1H, d), 8.08-8.20 (2H, m), 8.78-8.99 (2H, m), 9.02 (1H, d)

35

Example 51**1-[3-(Pyrid-3-yl-aminosulphonyl)-phenylcarbamoyl]5-methoxy-6-trifluoromethyl-indoline**

- 5 A suspension of 3-(pyrid-3-ylaminosulphonyl)-aminobenzene (D39) (0.5g, 2 mmol) in chloroform (40 ml) was treated with triethylamine (5 ml) and chlorotrimethylsilane (5 ml). The solution was evaporated to dryness, and the residue dissolved in dichloromethane (20 ml). Carbonyl diimidazole (0.32g, 2 mmol) was added and after 1 h the reaction mixture was evaporated to dryness. Dimethylformamide (20 ml) and
- 10 5-methoxy-6-trifluoromethyl indoline (0.43g, 2 mmol) was added, and the mixture heated to 100° C for 2 h. The cooled solution was diluted with water (60 ml). Filtration and drying afforded a brown solid (0.6g). Chromatography, eluting with 0-5% methanol in ethyl acetate afforded the product as a white solid (0.26g, 26%), m.p. >215° C.
- 15 ¹H NMR (DMSO) δ: 10.60 (1H, s), 8.9 (1H, s), 8.30 (1H, d, J2Hz), 8.25 (1H, dd, J5Hz, 2Hz), 8.20 (1H, t, J2Hz), 8.10 (1H, s), 7.80 (1H, d, J7Hz), 7.35-7.55 (3H, m), 7.30 (1H, m), 7.20 (1H, s), 4.20 (2H, t, J8Hz), 3.85 (3H, s), 3.25 (2H, t, J8Hz)

Example 52

- 20 **5-Methylthio-6-trifluoromethyl-1-[6-(pyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline**

- 5-Amino-2-(pyridin-3-yloxy)pyridine (0.5g, 2.7 mmol) in dichloromethane (25 ml) was treated with triethylamine (0.4 ml, 2.9 mmol) then phenyl chloroformate (0.34
- 25 ml, 2.7 mmol) dropwise at -20°C. The reaction mixture was allowed to warm to room temperature over 1 hour then poured into dilute aqueous sodium bicarbonate (50 ml). The organic phase was separated and the aqueous phase extracted with dichloromethane (2 x 50 ml). The combined organic phases were dried (Na₂SO₄) and evaporated to give the crude phenyl carbamate (0.84g) as a crystallising oil. This
- 30 material was taken-up in dry DMF (10 ml) and triethylamine (0.5 ml) and treated with 5-methylthio-6-trifluoromethyl indoline hydrochloride (0.63g, 2.32 mmol) at 100°C for 0.5 h. After cooling the DMF was removed under reduced pressure and the residue was partitioned between 5% aqueous sodium hydroxide (100 ml) and dichloromethane (3 x 100 ml). The combined organic extracts were dried (Na₂SO₄)
- 35 and evaporated. Chromatography using 2% methanol in ethyl acetate as eluant followed by recrystallisation from ethyl acetate/petroleum ether (60-80°) gave the title compound (0.88g, 73%) as a white crystalline solid m.p. 193-4°C.

¹H NMR (250 MHz, DMSO) δ: 3.28 (2H, t, J 8Hz), 3.37 (3H, s), 4.20 (2H, t, J 8Hz), 7.13 (1H, d, J 9Hz), 7.42-7.51 (2H, m), 7.61 (1H, m), 8.08 (1H, dd, J 8Hz, 2 Hz), 8.21 (1H, s), 8.27 (1H, d, J 2Hz), 8.40-8.48 (2H, m), 8.86 (1H, s).

MS (EI) m/e = 447 (MH⁺)

5

Example 53

5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline

- 10 5-Amino-2-(pyridin-3-yloxy)pyridine (0.2g, 1.1 mmol) was treated with phenyl chloroformate to give the phenyl carbamate which was treated with 5-methoxy-6-trifluoromethylindoline (0.23g, 1.1 mmol) according to the method of Example 52 to give the title compound (0.34g, 74%) as a white solid m.p. 202-4°C.

- 15 ¹H NMR (250 MHz, DMSO) δ: 3.28 (2H, t, J 8Hz), 3.86 (3H, s), 4.18 (2H, t, J 8Hz), 7.12 (1H, d, J 9Hz), 7.22 (1H, s), 7.47 (1H, dd, J 7Hz, 5Hz), 7.51 (1H, m, J 7Hz), 8.08 (1H, dd, J 8Hz, 2Hz), 8.10 (1H, s), 8.27 (1H, d, J 2Hz), 8.40-8.47 (2H, m), 8.78 (1H, s).

MS (EI) m/e = 431 (MH⁺)

20 Example 54

5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylmethyloxy)phenyl carbamoyl]indoline

- 25 4-(Pyridin-4-ylmethyloxy)aniline (0.5g, 2.5 mmol) was converted to the phenyl carbamate and treated with 5-methoxy-6-trifluoromethylindoline (0.54g, 2.5 mmol) as in the method of Example 52. Chromatography using ethyl acetate as eluant followed by recrystallisation from ethyl acetate/petroleum ether (60-80°) afforded the title compound (0.23g, 24%) as an off-white crystalline solid m.p. 205-207°C.

- 30 ¹H NMR (250 MHz, CDCl₃) δ: 3.26 (2H, t, J 8Hz), 3.82 (3H, s), 4.07 (2H, t, J 8Hz), 5.06 (2H, s), 6.29 (1H, s), 6.83 (1H, s), 6.91 (2H, d, J 10Hz), 7.28-7.48 (4H, m), 8.22 (1H, s), 8.60 (2H, d, J 7Hz).

MS (EI) m/e = 444 (MH⁺)

Example 55**5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-4-ylmethoxy)pyridin-3-ylcarbamoyl]indoline**

- 5 5-Amino-2-(pyridin-4-ylmethoxy)pyridine (0.5g, 2.5 mmol) was converted to the phenyl carbamate and treated with 5-methoxy-6-trifluoromethylindoline (0.54g, 2.5 mmol) as in the method of Example 52. Chromatography using ethyl acetate as eluant followed by recrystallisation from ethyl acetate/petroleum ether (60-80°C) afforded the title compound (0.13g, 13%) as an off-white solid m.p. 187-189°C.
- 10 ¹H NMR (250 MHz, CDCl₃) δ: 3.31 (2H, t, J 8Hz), 3.88 (3H, s), 4.12 (3H, t, J 8Hz), 5.40 (2H, s), 6.32 (1H, s), 6.88 (1H, m), 7.35 (2H, d, J 6Hz), 7.91 (1H, dd, J 8Hz, 2Hz), 8.04 (1H, d, J 2Hz), 8.22 (1H, s), 8.59 (2H, d, J 6Hz)
- MS (EI) m/e = 445 (MH⁺)

Example 56**5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-4-yl-methylamino carbonyl)phenyl carbamoyl]indoline**

- 20 This was prepared by the same methodology as for Example 69 affording the title compound in 11% yield as a white solid. m.p. 230-2°C.
- ¹H NMR (D6-DMSO) 2.50 (3H, s), 3.25 (2H, t), 3.45 (3H, s), 4.20 (2H, t), 7.15 (2H, d), 7.25 (2H, d), 7.50 (3H, m), 8.20 (1H, s), 8.45 (2H, d), 8.80 (1H, s)

Example 57

- 25 **Trans-5-Methylthio-6-trifluoromethyl-1-[4-[2-ethenyl-(4-pyridyl)]-phenyl carbamoyl]-indoline**

- 30 This was prepared from trans-4-[2-ethenyl-(4-pyridyl)]-aniline (D43) and 5-methylthio-6-trifluoromethyl indoline (D7) using the phenyl chloroformate procedure as for Description 18 and Example 26 affording the title compound as a yellow solid in 18% yield, m.p. 157-9°C.
- ¹H NMR (D6-DMSO) 2.50 (3H, s), 3.30 (2H, t), 4.25 (2H, t), 7.15 (1H, d), 7.45 (1H, s), 7.55 (2H, d), 7.65 (5H, m), 8.25 (1H, s), 8.55 (2H, d), 8.80 (1H, s)

Example 58**5-Methylthio-6-trifluoromethyl-1-{4-[2-ethyl(4-pyridyl)]phenyl carbamoyl}indoline**

- 5 This was prepared by hydrogenation of D42 followed by coupling with 5-methylthio-6-trifluoromethyl indoline (D7) using the phenyl chloroformate method, affording the title compound in 20% yield as a white solid, m.p. 158-161°C.

¹H NMR (DMSO) 2.50 (3H, s), 2.85 (4H, m), 3.25 (2H, t), 4.20 (2H, t), 7.15 (2H, d), 7.25 (2H, d), 7.45 (4H, m), 8.20 (1H, s), 8.45 (2H, d), 8.60 (1H, s).

10

Example 59**1-(1-(4-Pyridyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethylindoline**

- 15 The title compound was prepared by the method of Example 73, from aminoindole (D53). Yield 62%, m.p. 206-211°C

¹H NMR (CDCl₃) δ: 3.29 (2H, t, J=8), 3.85 (3H, s), 4.20 (2H, t, J=8), 6.78 (1H, d, J=3), 7.20 (1H, s), 7.41 (1H, dd, J=8,2), 7.72 (2H, d, J=6), 7.78 (1H, d, J=8), 7.83 (1H, d, J=3), 7.92 (1H, d, J=2), 8.16 (1H, s), 8.58 (1H, s), 8.70 (2H, d, J=6)
MS(API) m/z=453(MH⁺)

20

Example 60**5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylthiomethyl)phenyl carbamoyl]indoline**

- 25 4-(Pyridin-4-ylthiomethyl)aniline (0.37g, 1.71 mmol) was converted to the phenylcarbamate and treated with 5-methoxy-6-trifluoromethylindoline (D11) (0.37g, 1.71 mmol) as in the method of Example 26 to give the title compound (0.5g, 64%) as a white crystalline solid m.p. 174-5°C.

- ¹H NMR (250 MHz; DMSO) δ: 3.26 (2H, t, J 8Hz), 3.84 (3H, s), 4.16 (2H, t, J 8Hz), 4.32 (2H, s), 7.20 (1H, s), 7.32 (2H, d, J 7Hz), 7.37 (2H, d, J 8Hz), 7.52 (2H, d, J 8Hz), 8.11 (1H, s), 8.37 (2H, d, J 7Hz), 8.58 (1H, s).

30

MS(EI) m/e = 460 (MH⁺)

Example 61**5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylsulphonylmethyl)phenylcarbamoyl]indoline**

5 4-(Pyridin-4-ylsulphonylmethyl)aniline was converted to the title compound according the method of Example 60 to give a white crystalline solid (46%) m.p. 240-242°C.

¹H NMR (250 MHz; DMSO) δ: 3.26 (2H, t, J 8Hz), 3.84 (3H, s), 4.17 (2H, t, J 8Hz), 4.77 (2H, s), 7.08 (2H, d, J 8Hz), 7.20 (1H, s), 7.50 (2H, d, J 8Hz), 7.70 (2H, d, J 7Hz), 8.10 (1H, s), 8.59 (1H, s), 8.88 (2H, d, J 7Hz)
10 MS (EI) m/e = 492 (MH⁺)

Example 62**5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylmethylthio)phenylcarbamoyl]indoline**

4-(Pyridin-4-ylmethylthio)aniline was converted to the title compound according to the method of Example 60 to give a white crystalline solid (63%) m.p. 160-3°C.

¹H NMR (250 MHz; CDCl₃) δ: 3.27 (2H, t, J 8Hz), 3.85 (3H, s), 3.95 (2H, s), 4.08 (2H, t, J 8Hz), 6.41 (1H, s), 6.84 (1H, s), 7.12 (2H, d, J 7Hz), 7.23 (2H, d, J 8Hz), 7.33 (2H, d, J 8Hz), 8.21 (1H, s), 8.48 (2H, d, J 7Hz).
20 MS (EI) m/e = 460 (MH⁺)

Example 63**5-Methylthio-6-trifluoromethyl-1-[(6-phenoxy)-3-pyridylcarbamoyl]-indoline**

This was prepared from 6-phenoxy-3-aminopyridine and 5-methylthio-6-trifluoromethylindoline (D7) by similar methodology to Example 1, affording the title compound as a yellow solid in 39% yield, m.p. 86-88°C.

30 NMR (D6-DMSO) 2.50 (3H, s), 3.30 (2H, t), 4.20 (2H, t), 7.00 (1H, d), 7.10 (2H, m), 7.20 (1H, m), 7.45 (3H, m), 8.05 (1H, d), 8.20 (1H, s), 8.30 (1H, d), 8.85 (1H, s).

Example 64**5-Methoxy-6-trifluoromethyl-1-[2-(pyridin-3-yloxy)pyridin-4-ylcarbamoyl]indoline**

4-Amino-2-(pyridin-3-yloxy)pyridine (D45) was converted to the title compound by the method of Example 60 to give an off-white crystalline solid (89%) m.p. 223-5°C.

¹H NMR (250 MHz; DMSO) δ: 3.28 (2H, t, J 8Hz), 3.86 (3H, s), 4.21 (2H, t, J 8Hz), 7.24 (1H, s), 7.39 (1H, s), 7.40-7.52 (2H, m), 7.62 (1H, m, J 9Hz), 7.97 (1H, d, J 7Hz), 8.13 (1H, s), 8.40-8.48 (2H, m), 9.10 (1H, s).
MS (EI) m/e = 431 (MH⁺)

5

Example 65

5-Methylthio-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy) pyridin-3-ylcarbamoyl]indoline

10 5-Amino-2-(2-methylpyridin-3-yloxy)pyridine was converted to the title compound according to the method of Example 60 to give a pale yellow solid (30%) m.p. 204-7°C.

¹H NMR (250 MHz; DMSO) δ: 3.28 (2H, t, J 8Hz), 3.34 (3H, s), 4.19 (2H, t, J 8Hz), 7.10 (1H, d, 8 Hz), 7.31 (1H, dd, J 8Hz, 5Hz), 7.44-7.53 (2H, m), 8.06 (1H, dd, J 8Hz, 2Hz), 8.21 (1H, s), 8.32 (2H, d, J 5Hz), 8.82 (1H, s).
15 MS (EI) m/e = 461 (MH⁺)

Example 66

20 **5-Methylthio-6-trifluoromethyl-1-[6-(6-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline**

5-Amino-2-(6-methylpyridin-3-yloxy)pyridine was converted to the title compound according to the method of Example 60 to give an off-white solid (44%) m.p. 206-8°C.

25 ¹H NMR (250 MHz; DMSO) δ: 3.28 (2H, t, J 8Hz), 3.37 (3H, s), 4.19 (2H, t, J 8Hz), 7.09 (1H, d, J 7Hz), 7.32 (1H, d, J 7Hz), 7.45-7.53 (2H, m), 8.06 (1H, dd, J 7Hz, 2Hz), 8.20 (1H, s), 8.24 (1H, d, J 2Hz), 8.30 (1H, d, J 2Hz), 8.84 (1H, s).
MS (EI) m/e = 461 (MH⁺)

Example 67

30 **5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-3-ylthio)pyridin-3-ylcarbamoyl]indoline**

35 5-Amino-2-(pyridin-3-ylthio)pyridine was converted to the title compound according to the method of Example 60 to give a white crystalline solid (51%) m.p. 208-210°C.
¹H NMR (250 MHz; DMSO) δ: 3.28 (2H, t, J 8Hz), 3.85 (3H, s), 4.17 (2H, t, J 8Hz), 7.20 (1H, d, J 7Hz), 7.22 (1H, s), 7.49 (1H, dd, J 7Hz, 5Hz), 7.90-7.99 (2H, m), 8.11 (1H, s), 8.57-8.68 (3H, m), 8.84 (1H, s).

MS(EI) m/e = 447 (MH⁺)

Example 68

5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-3-ylmethyl)amidophenylcarbamoyl]indoline

This was prepared in 61% yield by the same method as for Example 69, m.p. >250° C.

¹H NMR (D6-DMSO) δ: 2.50 (3H, s), 3.30 (2H, t), 4.25 (2H, t), 4.50 (2H, d), 7.40 (1H, m), 7.50 (1H, s), 7.70 (3H, m), 7.85 (2H, d), 8.25 (1H, s), 8.45 (1H, m), 8.55 (1H, m), 8.80 (1H, s), 9.00 (1H, t)

Example 69

5-Methylthio-6-trifluoromethyl-1-[3-(pyrid-4-ylmethyl)amidophenylcarbamoyl]indoline

A suspension of 5-methylthio-6-trifluoromethyl-1-(3-carboxyphenyl carbamoyl) indoline (D55) (0.5g, 1.26 mmol) in dichloromethane (10 ml) was treated with oxalyl chloride (0.2 ml, 0.3g, 2.4 mmol) and N,N-dimethyl formamide (3 drops). After 1h the reaction mixture was evaporated to dryness. The residue was dissolved in tetrahydrofuran (20 ml) and added to a solution of 4-aminomethyl pyridine (0.15 ml, 1.39 mmol) and triethylamine (0.2 ml, 0.15g, 1.5 mmol) in tetrahydrofuran (10 ml) at 0°C. After 1 h 5M aqueous sodium hydroxide solution (5 ml) was added, followed by water (20 ml). Filtration and drying afforded the product as a yellow solid (0.58g, 94%) m.p. 122-3°C.

¹H NMR (D6-DMSO) δ: 2.50 (3H, s), 3.30 (2H, t), 4.20 (2H, t), 4.50 (2H, d), 7.30 (2H, d), 7.40 (1H, t), 7.45 (1H, s), 7.60 (1H, d), 7.80 (1H, d), 8.05 (1H, s), 8.25 (1H, s), 8.50 (2H, d), 8.85 (1H, bs), 9.15 (1H, t)

Example 70

5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-2-ylmethyl)amidophenylcarbamoyl]indoline

This was prepared by the same method as for Example 69, affording the title compound as a white solid in 84% yield, m.p. 203-5°C.

¹H NMR (D6-DMSO) δ: 2.50 (3H, s), 3.30 (2H, t), 4.20 (2H, t), 4.55 (2H, d), 7.25-7.35 (2H, m), 7.45 (1H, s), 7.65-7.75 (3H, m), 7.90 (2H, d), 8.25 (1H, s), 8.50 (1H, d), 8.85 (1H, s), 9.00 (1H, t).

Example 71**1-(1-(3-Pyridylmethyl)-5-indolylcarbonyl)-5-methoxy-6-trifluoromethylindoline**

5 A solution of aminoindole (D48, 0.40g, 1.8 mmol) and 1,1'-carbonyldiimidazole (0.30g, 1.8 mmol) in dichloromethane (40 mL) was stirred at room temperature for 1.75 h, then evaporated. To the residue was added dimethylformamide (DMF, 10 mL) and a solution of 5-methoxy-6-trifluoromethylindoline (D11, 0.39g, 1.8 mmol) in DMF (5mL). The mixture was stirred at 110°C overnight, then poured into water and extracted with dichloromethane. The extract was washed with water, dried and evaporated. The residue was triturated with ether to give a grey solid, which was recrystallised from dichloromethane/methanol to give the title compound (0.15g, 18%) m.p. 243-6°C.

15 ¹H NMR (CDCl₃) δ: 3.26 (2H, t, J=8), 3.83 (3H, s), 4.17 (2H, t, J=8), 5.45 (2H, s), 6.45 (1H, d, J=3), 7.19 (1H, s), 7.22 (1H, d, J=8), 7.33 (1H, dd, J=7,5), 7.42 (1H, d, J=8), 7.51 (1H, d, J=3), 7.5 (1H, d, J=8), 7.72 (1H, s), 8.12 (1H, s), 8.41 (1H, s), 8.46 (1H, d, J=5), 8.51 (1H, s)

MS(API) m/z=467 (MH⁺)

20

Example 72**1-(1-(4-Pyridylmethyl)-5-indolylcarbonyl)-5-methoxy-6-trifluoromethylindoline**

25 A mixture of aminoindole (D49, 0.46g, 2.1 mmol), phenyl chloroformate (0.26 mL, 2.1 mmol) and triethylamine (0.29 mL, 2.1 mmol) in dichloromethane (5 mL) was stirred at room temperature for 1 h. The mixture was then diluted with dichloromethane, washed with water, dried and evaporated. The residue was dissolved in acetonitrile (10 mL). 5-Methoxy-6-trifluoromethylindoline (D11, 0.45g, 2.1 mmol) and triethylamine (0.29 mL, 2.1 mmol) were added and the mixture was stirred for 3h at room temperature. The reaction was worked up as for Example 71, and the solid obtained after trituration was recrystallised from dichloromethane/petrol to give the title compound (0.26g, 27%), m.p. 215-8°C.

30 ¹H NMR (CDCl₃) δ: 3.26 (2H, t, J=8), 3.83 (3H, s), 4.16 (2H, t, J=8), 5.48 (2H, s), 6.49 (1H, d, J=3), 7.04 (2H, d, J=6), 7.20 (2H, m), 7.30 (1H, d, J=8), 7.49 (1H, d, J=3), 7.73 (1H, s), 8.12 (1H, s), 8.42 (1H, s), 8.47 (2H, d, J=6).

MS(API) m/z=467 (MH⁺)

35

Example 73**1-(1-(3-pyridyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline**

The title compound was prepared by the method of Example 72, from aminoindoline
 5 (D52, 0.34g, 1.63 mmol). Addition of the reaction mixture to water gave a precipitate which was filtered off, dried and recrystallised from dichloromethane/petrol to give the title compound (0.61g, 84%), m.p. 202-4°C.
¹H NMR (CDCl₃) δ: 3.28 (2H, t, J=8), 3.84 (3H, s), 4.19 (2H, t, J=8), 6.73 (1H, d, J=3), 7.21 (1H, s), 7.38 (1H, dd, J=8,2), 7.55 (1H, d, J=8), 7.62 (1H, dd, J=7,5), 7.73
 10 (1H, d, J=3), 7.89 (1H, d, J=2), 8.09 (1H, d, J=7), 8.17 (1H, s), 8.55 (1H, s), 8.60 (1H, d, J=5), 8.89 (1H, d, J=2).
 MS(API) m/z=453(MH⁺)

Example 74**15 5-Methylthio-6-trifluoromethyl-1-{3-[2-(3-pyridyl)thiazol-4-yl]phenylcarbamoyl} indoline**

A solution of 4-(3-aminophenyl)-2-(3-pyridyl)-thiazole (0.76g, 3 mmol) in
 chloroform (30 ml) was added to a solution of carbonyl diimidazole (0.49g, 3 mmol)
 20 in dichloromethane (10 ml). After 1 h the mixture was evaporated. 5-Methylthio-6-trifluoromethyl indoline (0.7g, 3 mmol) and N,N-dimethylformamide (20 ml) were added. The mixture was heated at 100°C for 1h, then diluted with water (50 ml). Filtration and evaporated afforded a yellow solid (1.1g). Recrystallisation from ethyl acetate-petrol afforded the title compound as a white solid (0.53g, 35%), m.p. 154-
 25 5°C.
¹H NMR (DMSO) 2.50 (3H, s), 3.30 (2H, t), 4.25 (2H, t), 7.45 (1H, t), 7.50 (1H, s), 7.55 (2H, m), 7.70 (1H, m), 8.25 (2H, m), 8.40 (1H, dt), 8.70 (1H, d), 8.80 (1H, s), 9.25 (1H, d).

30 Example 75**5-Methylthio-6-trifluoromethyl-1-{4-[2-(4-pyridyl)-thiazol-4-yl]phenyl carbamoyl}indoline**

This was prepared in the same manner as 5-methylthio-6-trifluoromethyl-1-{3-[2-(3-
 35 pyridyl)-thiazol-4-yl]phenyl carbamoyl} indoline to give the product as a yellow solid (0.2g, 31%), m.p. 253-4° C.
¹H NMR (DMSO) δ: 8.8 (3H, m), 8.2 (2H, s), 8.0 (4H, m), 7.7 (2H, d), 7.4 (1H, s), 4.2 (2H, t), 3.3 (2H, t), 2.5 (3H, s)

Example 76**5-Methylthio-6-trifluoromethyl-1-{4-[2-(3-pyridyl)-thiazol-4-yl]phenylcarbamoyl}indoline**

5

This was prepared in the same manner as 5-methylthio-6-trifluoromethyl-1-{3-[2-(3-pyridyl)-thiazol-4-yl]phenyl carbamoyl} indoline to give the product as a yellow solid (0.25g, 39%), m.p. > 250° C.

¹H NMR (DMSO) δ: 9.2 (1H, s), 8.8 (1H, s), 8.7 (1H, d), 8.4 (1H, d), 8.2 (1H, s), 8.1 (1H, s), 7.95 (2H, d), 7.7 (2H, d), 7.6 (1H, q), 7.4 (1H, s), 4.2 (2H, t), 3.3 (2H, t), 2.5 (3H, s)

Example 77**1-[4-Fluoro-3-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline**

15

A solution of 4-fluoro-3-(pyrid-3-yl)phenylcarbonyl azide (D59) (270 mg, 1.1 mmol) in toluene (10 ml) was refluxed under argon for 45 minutes and cooled. To a stirred solution of the indoline (D11) (266 mg, 1.1 eq) in dichloromethane was added the isocyanate solution. The total solution was stirred at room temperature overnight, evaporated to dryness and chromatographed (EtOAc→5% MeOH/EtOAc, SiO₂). Concentration of fractions afforded the title compound as a white powder (315 mg, 66%). Melting point = 210°-212°C

¹H NMR (250 MHz, δ: 8.73 (d, 2H), 8.60 (dd, 1H), 8.10 (s, 1H), 7.97 (dd, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 7.54 (m, 1H), 7.30 (t, 1H), 7.21 (s, 1H), 4.15 (t, 2H), 3.83 (s, 3H), 3.27 (t, 2H).

Mass spec: m/z = 432 MH⁺

Example 78**1-[3-Fluoro-5-(pyrimidin-5-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline**

30

3-Fluoro-5-(pyrimidin-5-yl)phenylcarbonyl azide (D60) (0.22g, 0.00091 mole) was dissolved in dry toluene (15 ml) and heated under reflux under argon for ½ hour. After cooling to ambient temperature, 5-methoxy-6-trifluoromethyl indoline (D11) (0.20g, 0.00091 mole) in dichloromethane (8 ml) was added and the mixture stirred for 18 h. The dichloromethane was removed *in vacuo* and the resulting precipitate

35

filtered and dried *in vacuo*. This was recrystallised from ethyl acetate/60-80° petroleum ether to afford the title compound (0.17g, 43%).

¹H NMR (200 MHz, D²O) δ (ppm): 3.30 (2H, t, J=8), 3.87 (3H, s), 4.20 (2H, t, J=8), 7.22 (1H, s), 7.38 (1H, dt, J=3, 9), 7.68 (1H, dt, J=3, 11), 7.79 (1H, s), 8.14 (1H, s), 8.90 (1H, s), 9.12 (2H, s), 9.24 (1H, s).

Example 79

1-[4-Chloro-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline

10

4-Chloro-3-(4-methyl-3-pyridyl)aniline (D62) was converted to the phenyl carbamate in the usual manner and then treated with 5-methoxy-6-trifluoromethylindoline (D11). Purification of the residue obtained by flash chromatography on silica gel gave the title compound (E79) (0.115g, 49%) m.p. 140-141°C.

15 ¹H NMR (CDCl₃) δ: 2.19 (3H, s), 3.28 (2H, t, J=8Hz), 3.82 (3H, s), 4.15 (2H, t, J=8Hz), 6.81 (1H, s), 7.09 (1H, s), 7.20 (1H, d, J=6Hz), 7.25 (1H, s), 7.40 (1H, d, J=8Hz), 7.52-7.59 (1H, m), 8.20 (1H, s), 8.30 (1H, s), 8.45 (1H, d, J=6Hz).

Example 80

20 1-[2,3-Dihydro-7-(pyrid-3-yl)benzofuran-5-ylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline

Phenyl N-[2,3-dihydro-7-(pyrid-3-yl)benzofuran-5-yl]carbamate (D65) (0.20g, 0.00060mole) in dry DMF (10 ml) was treated under argon with 5-methoxy-6-trifluoromethyl indoline (D11) (0.13g, 0.00060 mole) and heated under reflux for 18 hours. The reaction was allowed to cool to ambient temperature and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane, washed with deionised water and 10% sodium hydroxide solution, dried (Na₂SO₄) and evaporated *in vacuo*. The resulting brown oil was purified by flash column chromatography on silica gel, eluting with 2% methanol/dichloromethane, followed by recrystallisation from ethyl acetate 60-80° petroleum ether to afford the title compound (0.07g, 26%) as a beige solid.

30 ¹H NMR (200 MHz, D²O) δ (ppm): 3.12-3.49 (4H, m), 3.85 (3H, s), 4.15 (2H, t, J=8), 4.61 (2H, t, J=10), 7.21 (1H, s), 7.40-7.58 (3H, m), 8.07 (1H, dt, J=1, 7), 8.13 (1H, s), 8.43-8.60 (2H, m), 8.88 (1H, d, J=1).

Example 81

5-Methoxy-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yl)pyridin-3-ylcarbamoyl]indoline

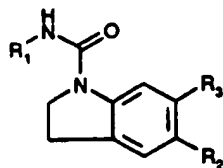
- 5 5-Amino-2-(2-methylpyridin-3-yloxy)pyridine was converted to the title compound according to the method of Example 60 to give a white crystalline solid (71%) m.p. 227-230°C.
- ¹H NMR (250 MHz, DMSO) δ : 3.28 (2H, t, J8Hz), 3.85 (3H, s), 4.15 (2H, t, J8Hz), 7.09 (1H, d, J8Hz), 7.21 (1H, s), 7.30 (1H, dd, J8Hz, 5Hz), 7.49 (1H, d, J8Hz), 8.04 (1H, dd, J8Hz, 2Hz), 8.10 (1H, d, J2Hz), 8.32 (1H, d, J5Hz), 8.72 (1H, s).
- 10 MS(EI) m/e=445 (MH⁺)

Example 82

- 15 **5-Methoxy-6-trifluoromethyl-1-[6-(4-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline**

- 5-Amino-2-(4-methylpyridin-3-yloxy)pyridine was converted to the title compound according to the method of Example 60 to give a white crystalline solid (51%) m.p. 188-191°C.
- 20 ¹H NMR (250 MHz, DMSO) δ : 3.30 (2H, t, J8Hz), 3.83 (3H, s), 4.15 (2H, t, J8Hz), 7.10 (1H, d, J8Hz), 7.20 (1H, s), 7.38 (1H, d, J5Hz), 8.04 (1H, dd, J8Hz, 2Hz), 8.10 (1H, s), 8.17 (1H, d, J2Hz), 8.29 (1H, s), 8.30 (1H, d, J5Hz), 8.72 (1H, s).
- MS (EI) m/e = 445 (MH⁺)

- 25 The following examples were prepared using similar techniques:



Exam ple No.	R ₁	R ₂	R ₃	M.Pt. °C
83	3-(3-Pyridyl)phenyl	OMe	CF ₃	192-193
84	2-Methoxy-3-(3-pyridyl)phenyl	OMe	CF ₃	196-197
85	2-Chloro-3-(3-pyridyl)phenyl	OMe	CF ₃	214-216
86	3-(3-Quinolyl)phenyl	OMe	CF ₃	240 (dec.)

87	5-(4-Fluorophenyl)-3-pyridyl	OMe	CF ₃	>200
88	5-(3,5-Difluorophenyl)-3-pyridyl	OMe	CF ₃	226-229
89	5-(4-Chlorophenyl)-3-pyridyl	OMe	CF ₃	198-199
90	5-(2-Methylphenyl)-3-pyridyl	OMe	CF ₃	103-105
91	5-(2-Formylphenyl)-3-pyridyl	OMe	CF ₃	114-116
92	5-(2-Hydroxymethylphenyl)-3-pyridyl	OMe	CF ₃	190-192
93	5-(3-Chloro-4-fluorophenyl)-3-pyridyl	OMe	CF ₃	113-115
94	6-Phenyl-3-pyridyl	OMe	CF ₃	204-207
95	5-(3-pyridyl)-2-pyridyl	OMe	CF ₃	>225
96	6-(1-Pyrazolyl)-3-pyridyl	OMe	CF ₃	>225
97	3-(4-N,N-Dimethylaminophenyl)phenyl	OMe	CF ₃	213-215
98	3-(4-N,N-Dimethylaminomethylphenyl)phenyl	OMe	CF ₃	209-211
99	3-(3-N,N-Dimethylaminomethylphenyl)phenyl	OMe	CF ₃	185-187
100	3-(5-N,N-Dimethylaminomethyl-1,2,4-oxadiazol-3-yl)phenyl	OMe	CF ₃	154-155
101	3-(1-Dimethylaminoethyl-2-pyrrolyl)phenyl	OMe	CF ₃	158-159
102	3-(2-Pyrrolyl)phenyl	OMe	CF ₃	>240
103	3-(3-Pyridyl)phenyl	Me	Cl	208-210
104	5-Ethenyl-3-(3-pyridyl)phenyl	OMe	CF ₃	138-140
105	3-(3-Pyridyl)-5-(trifluoromethyl)phenyl	OMe	CF ₃	220-222
106	5-Chloro-3-(3-pyridyl)phenyl	OMe	CF ₃	183-185
107	5-Acetyl-3-(3-pyridyl)phenyl	OMe	CF ₃	174-176
108	4-Methoxy-3-(3-pyridyl)-5-(trifluoromethyl)phenyl	OMe	CF ₃	180-181
109	4-Methyl-3-(4-methyl-3-pyridyl)phenyl	OMe	CF ₃	153-155
110	3-(2-Methyl-3-pyridyl)phenyl	OMe	CF ₃	179-180
111	3-(2,4-Dimethyl-3-pyridyl)phenyl	OMe	CF ₃	202-204
112	3-(6-Methyl-3-pyridyl)phenyl	OMe	CF ₃	228-230
113	3-(2-Methyl-4-pyrimidinyl)phenyl	OMe	CF ₃	>220
114	3,5-(Di-3-pyridyl)phenyl	OMe	CF ₃	155-156
115	3-(3-Pyridyl)-5-(4-pyridyl)phenyl	OMe	CF ₃	153-154
116	5-Fluoro-3-(6-methyl-3-pyridyl)phenyl	OMe	CF ₃	213-215
117	3-(4,6-Dimethyl-3-pyridyl)phenyl	OMe	CF ₃	161-162
118	5-Fluoro-3-(3-pyridazinyl)phenyl	OMe	CF ₃	230-231

119	3-(5-Pyrimidinyl)phenyl	OMe	CF ₃	245-250
120	3-(2-Pyrazinyl)phenyl	OMe	CF ₃	208-209
121	3-(6-Methyl-3-pyridazinyl)phenyl	OMe	CF ₃	229-231
122	3-(3-Pyridyl)-5-(trifluoromethoxy)phenyl	OMe	CF ₃	168-170
123	3-(3-Pyridyl)-4-(trifluoromethoxy)phenyl	OMe	CF ₃	99-100
124	5-Fluoro-4-methyl-3-(3-pyridyl)phenyl	OMe	CF ₃	244-247
125	5-Fluoro-3-(2-methyl-3-pyridyl)phenyl	OMe	CF ₃	204-205
126	5-Fluoro-3-(2-pyrazinyl)phenyl	OMe	CF ₃	230-231
127	5-Fluoro-3-(4,6-dimethylpyrid-3-yl)phenyl	OMe	CF ₃	215-218
128	5-Fluoro-4-methyl-3-(pyrimidin-3-yl)phenyl	OMe	CF ₃	188-189
129	5-Fluoro-4-methyl-3-(pyrid-3-yl)phenyl	Me	Cl	233-235
130	5-(5-Pyrimidinyl)-3-pyridyl	OMe	CF ₃	120-121, 215-216
131	5-Fluoro-3-(2-pyrazinyl)phenyl	Me	Cl	226-227
132	5-Fluoro-3-(5-pyrimidinyl)phenyl	Me	Cl	222-226
133	3-(3-Pyridyl)phenyl	C(Me) ₂ CH ₂ CH ₃		91-92
134	5-Fluoro-3-(2-methyl-3-pyridyl)phenyl	Me	Cl	205-206
135	4-Fluoro-3-(3-pyridyl)phenyl	Cl	Cl	200-202
136	4-Fluoro-3-(3-pyridyl)phenyl	Me	Cl	185-186
137	3-(Pyrid-3-ylmethyloxy)phenyl	OMe	CF ₃	202-204
138	4-(Pyrid-3-ylmethyloxy)phenyl	OMe	CF ₃	215-217
139	3-(Pyrid-3-yloxymethyl)phenyl	OMe	CF ₃	188-190
140	5-Methyl-6-(pyrid-3-yl)pyrid-3-yl	OMe	CF ₃	230-232
141	5-Chloro-6-(pyrid-3-yl)pyrid-3-yl	SMe	CF ₃	245-250
142	6-(5-Chloropyrid-3-yl)pyrid-3-yl	SMe	CF ₃	193-195
143	4-(Pyrid-3-yloxy)phenyl	OMe	CF ₃	193-194
144	6-(Pyrid-3-ylthio)pyrid-3-yl	SMe	CF ₃	204-206
145	6-(Pyrid-4-ylthio)pyrid-3-yl	SMe	CF ₃	214-216
146	6-(Pyrid-4-ylthio)pyrid-3-yl	OMe	CF ₃	204-206
147	4-(Pyrid-4-ylmethyl)phenyl	SMe	CF ₃	206-209
148	3-(Pyrid-3-ylmethylaminocarbonyl)phenyl	SMe	CF ₃	210-215
149	3-[3-(Pyrid-2-yl)propionyl]phenyl	SMe	CF ₃	145-146
150	3-[3-(Pyrid-2-yl)-1-hydroxypropyl]phenyl	SMe	CF ₃	78-80
151	4-(Pyrid-4-ylmethylaminocarbonyl)phenyl	SMe	CF ₃	138-140
152	3-[1-(Pyrid-2-yl)propionyl]phenyl	SMe	CF ₃	110-112

153	3-[2-(Pyrid-2-yl)ethylcarbamoyl]phenyl	SMe	CF ₃	92-94
154	3-[(Pyrid-2-yl)methylcarbamoyl]phenyl	SMe	CF ₃	116-118
155	6-(Phenoxy)pyrid-3-yl	OMe	CF ₃	202-203
156	6-(2,4-Dimethylpyrid-3-yloxy)pyrid-3-yl	OMe	CF ₃	218-221
157	6-(2-Methylphenoxy)pyrid-3-yl	OMe	CF ₃	226-228
158	6-(3-Methoxyphenoxy)pyrid-3-yl	OMe	CF ₃	188-189
159	6-(4-Fluoro-2-methylphenoxy)pyrid-3-yl	OMe	CF ₃	208-209
160	6-(2,4-Dimethylphenoxy)pyrid-3-yl	OMe	CF ₃	236-238
161	6-(2-Chloropyrid-3-yloxy)pyrid-3-yl	OMe	CF ₃	238-240
162	6-(2-Ethylphenoxy)pyrid-3-yl	OMe	CF ₃	215-220
163	6-(4-Carbamoylphenoxy)pyrid-3-yl	OMe	CF ₃	245-248
164	6-(2-Trifluoromethylphenoxy)pyrid-3-yl	OMe	CF ₃	237-238
165	6-(3-Trifluoromethylphenoxy)pyrid-3-yl	OMe	CF ₃	193-194
166	6-(2,6-Dimethylpyrid-3-yloxy)pyrid-3-yl	OMe	CF ₃	230-233
167	6-(2-Methylpyrid-3-yloxy)pyrid-3-yl	Me	Cl	181-183
168	6-(2-Methylpyrid-3-yloxy)pyrid-3-yl	Cl	Cl	225-228
169	4-Fluoro-3-(5-pyrimidinyl)phenyl	Cl	Cl	132-135
170	5-Fluoro-3-(5-pyrimidinyl)phenyl	Cl	Cl	260
171	4-Fluoro-3-(5-pyrimidinyl)phenyl	Me	Cl	211-213
172	5-Fluoro-3-(5-pyrimidinyl)phenyl	Br	CF ₃	214-218
173	6-(2-Methyl-1-oxopyrid-3-yloxy)pyrid-3-yl	OMe	CF ₃	252-257
174	4-Fluoro-3-(3-pyridyl)phenyl	Br	CF ₃	200-201
175	6-(3-Cyanophenoxy)pyrid-3-yl	OMe	CF ₃	136-138
176	6-(4-Cyanophenoxy)pyrid-3-yl	OMe	CF ₃	188-189
177	6-(2-Methylpyrid-3-yloxy)pyrid-3-yl	Br	CF ₃	211-213

Pharmacological data

[³H]-mesulergine binding to rat r human 5-HT_{2C} clones expressed in 293 cells in vitro

5

Compounds were tested following the procedure outlined in WO 94/04533. The compounds of examples 1 to 165 have pK_i values of 5.8 to 9.7.

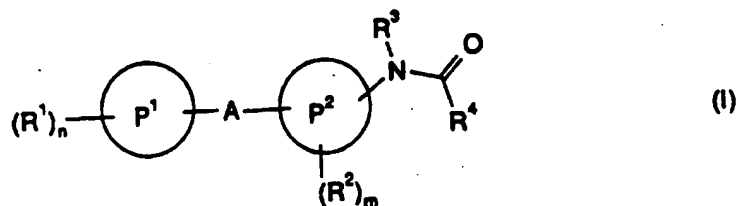
Reversal of MCPP-induced Hypolocomotion

- 10 Compounds were tested following the procedure outlined in WO 94/04533. The compound of examples 1, 3, 7, 8, 21, 24, 25, 26, 31, 40, 42, 52, 53, 54, 55, 77, 78, 79, 80 and 81 have ID₅₀'s between 0.5 and 5.5 mg/kg p.o.

15

Claims:

1. A compound of formula (I) or a salt thereof:



5

wherein:

- 10 P¹ and P² are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

A is a bond, a chain of 1 to 5 atoms optionally substituted by C₁₋₆ alkyl or A is an optionally substituted phenyl or an optionally substituted 5- to 7-membered heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

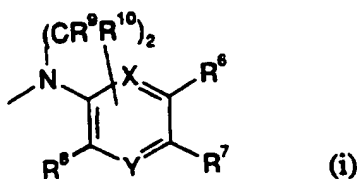
- 15 R¹ and R² groups are each independently hydrogen, C₁₋₆ alkyl optionally substituted by NR¹²R¹³, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylthio, cyano, nitro, halogen, CF₃, C₂F₅, NR¹²R¹³, CONR¹²R¹³, NR¹²COR¹³, S(O)_pNR¹²R¹³, CHO, OCF₃, SCF₃, COR¹⁴, CH₂OR¹⁴, CO₂R¹⁴ or OR¹⁴ where p is 1 or 2 and R¹², R¹³ and R¹⁴ are independently hydrogen, C₁₋₆ alkyl, optionally substituted aryl or optionally

- 20 substituted arylC₁₋₆alkyl;

n and m are independently 0, 1 or 2;

R³ is hydrogen or C₁₋₆ alkyl;

R⁴ is a group of formula (i):



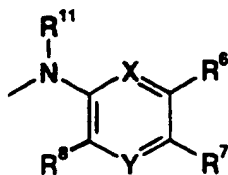
25

in which:

X and Y are both nitrogen, one is nitrogen and the other is carbon or a CR⁵ group or one is a CR⁵ group and the other is carbon or a CR⁵ group;

- 30 R⁵, R⁶, R⁷ and R⁸ groups are independently hydrogen, C₁₋₆ alkyl optionally substituted by one or more fluorine atoms, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl, C₃₋₆

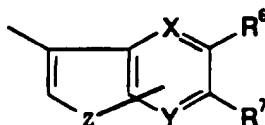
- cycloalkyl-C₁₋₆alkoxy, C₂₋₆ alkynyl, C₃₋₆ cycloalkyloxy, C₃₋₆ cycloalkyl-C₁₋₆ alkyl, C₁₋₆ alkylthio, C₃₋₆ cycloalkylthio, C₃₋₆ cycloalkyl-C₁₋₆ alkylthio, C₁₋₆alkoxy, hydroxy, halogen, nitro, OCF₃, SCF₃, SO₂CF₃, SO₂F, formyl, C₂₋₆ alkan yl, cyano, optionally substituted phenyl or thienyl, NR¹²R¹³, CONR¹²R¹³ or
 5 CO₂R¹⁴ where where R¹², R¹³ and R¹⁴ are as defined for R¹; or R⁶ and R⁷ form part of an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring; R⁹ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl; or R⁴ is a group of formula (ii):



10

(ii)

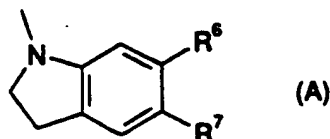
- in which X and Y are both nitrogen, one is nitrogen and the other is a CR⁵ group or X
 15 and Y are both CR⁵ groups and R⁵, R⁶, R⁷ and R⁸ are as defined in formula (I); and R¹¹ is hydrogen or C₁₋₆ alkyl, or R⁴ is a group of formula (iii):



20

(iii)

- in which R⁶, R⁷, X and Y are as defined in formula (i) and Z is O, S, CH₂ or NR¹⁵ where R¹⁵ is hydrogen or C₁₋₆ alkyl.
 2. A compound according to claim 1 in which A is a bond or a group CH₂O,
 25 OCH₂, or O.
 3. A compound according to claim 1 or 2 in which R² is hydrogen, halogen, methyl, CF₃ or OCF₃.
 4. A compound according to any one of claims 1 to 3 in which R³ is hydrogen.
 5 A compound according to any one of claims 1 to 4 in which R⁴ is a group of
 30 formula (i):



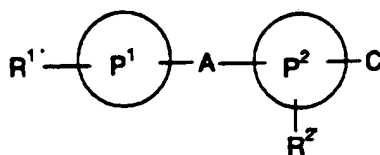
in which R⁶ and R⁷ are as defined in formula (i).

- 6 A compound according to any one of claims 1 to 5 in which R⁶ is
 5 trifluoromethyl or halogen and R⁷ is C₁₋₆ alkox, C₁₋₆alkylthio or C₁₋₆ alkyl.
7. A compound according to claim 1 which is:
- 1-[(3-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[(4-Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline,
 1-[(3-Pyridyl)-3-phenyl carbamoyl]-5-methylthio-6-trifluoromethyl indoline,
 10 1-[(3-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[(4-Pyridyl)-4-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[(2-Pyridyl)-3-phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[4-Methyl-3-(3-Pyridyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[3-Fluoro-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 15 1-[2-Fluoro-5-(3-pyridyl) phenyl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methoxy-6-trifluoromethyl indoline,
 1-(5-Phenyl pyrid-3-yl carbamoyl)-5-methylthio-6-trifluoromethyl indoline,
 1-[5-(3-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[5-(4-Trifluoromethylphenyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl
 20 indoline,
 1-[5-(4-Methylphenyl)-pyrid-3yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[5-(2-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[5-(3-Thienyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[5-(2-Pyrrolyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 25 1-[5-(4-Pyridyl)-pyrid-3-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[2-(3-Pyridyl)-thiazol-4-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[2-(2-Pyridyl)-thien-5-yl carbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-(3-Fluoro-5-(4-methyl-3-pyridyl)phenylcarbamoyl)-5-methoxy-6-
 trifluoromethylindoline,
 30 1-(5-(2,6-Difluorophenyl)-3-pyridylcarbamoyl)-5-methoxy-6-
 trifluoromethylindoline,
 6-Chloro-5-methyl-1-(4-methyl-3-(pyrid-3-yl)-phenylcarbamoyl) indoline,
 1-(4-Methyl-3-(pyrid-3-yl) phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl
 indoline,

- 1-(3-Fluoro-5-(pyrid-3-yl)phenylcarbamoyl)-5-thiomethyl-6-trifluoromethyl-indoline,
 1-(4-Chloro-3-(pyrid-3-yl)phenylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
 5 5-Methoxy-1-(5-methyl-(1,2,4-oxadiazol-3-yl)-phenylcarbamoyl)-6-trifluoromethyl indoline,
 1-[4-Methyl-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,
 1-[5-Bromo-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[4-t-Butyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 10 1-[4-Methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[5-Fluoro-4-methoxy-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[3-Bromo-4-methyl-5-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 15 1-[3-(4-Isoquinolyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[5-(4-Methyl-3-pyridyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[6-(3-Pyridyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[5-(2-Furyl)-pyrid-3-ylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 20 1-[2-(Pyrazinyl)-thiazol-4-ylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,
 1-[3-(5-Pyrimidyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,
 1-[3-(4-Methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 1-[5-Ethyl-3-(pyrid-3-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 5-Methoxy-1-[5-phenyl-3-(pyrid-3-yl)phenylcarbamoyl]-6-trifluoromethyl indoline,
 25 6-Chloro-5-methyl-1-[4-methyl-3-(4-methyl-3-pyridyl)phenyl carbamoyl] indoline,
 1-[3-(pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,
 1-[3-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl-indoline,
 30 1-[3-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline,
 1-[4-(Pyrid-3-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl indoline,
 1-[4-(Pyrid-4-ylaminocarbonyl)-phenylcarbamoyl]-5-methylthio-6-trifluoromethyl
 35 indoline,
 1-[3-(3-pyridylcarbonyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[3-(Pyrid-3-yl-aminosulphonyl)-phenylcarbamoyl]-5-methoxy-6-trifluoromethyl-indoline,

- 5-Methylthio-6-trifluoromethyl-1-[6-(pyridin-3-yl xy)pyridin-3-ylcarbamoyl]indoline,
 5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylmethyloxy)phenyl
 5 carbamoyl]indoline,
 5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-4-ylmethyloxy)pyridin-3-ylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-4-yl-methylamino carbonyl)phenyl
 carbamoyl]indoline,
 10 Trans-5-Methylthio-6-trifluoromethyl-1-[4-[2-ethenyl-(4-pyridyl)]-phenyl
 carbamoyl]-indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-[2-ethyl(4-pyridyl)]phenyl carbamoyl]indoline,
 1-(1-(4-Pyridyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylthiomethyl)phenyl
 15 carbamoyl]indoline,
 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylsulphonylmethyl)
 phenylcarbamoyl]indoline,
 5-Methoxy-6-trifluoromethyl-1-[4-(pyridin-4-ylmethylthio)phenyl
 carbamoyl]indoline,
 20 5-Methylthio-6-trifluoromethyl-1-[(6-phenoxy)-3-pyridylcarbamoyl]-indoline,
 5-Methoxy-6-trifluoromethyl-1-[2-(pyridin-3-yloxy)pyridin-4-ylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy) pyridin-3-ylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[6-(6-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 25 5-Methoxy-6-trifluoromethyl-1-[6-(pyridin-3-ylthio)pyridin-3-ylcarbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-3-ylmethyl)amido phenyl
 carbamoyl]indoline,
 5-Methylthio-6-trifluoromethyl-1-[3-(pyrid-4-ylmethyl) amidophenylcarbamoyl]
 30 indoline,
 5-Methylthio-6-trifluoromethyl-1-[4-(pyrid-2-ylmethyl) amidophenylcarbamoyl]
 indoline,
 1-(1-(3-Pyridylmethyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
 1-(1-(4-Pyridylmethyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethylindoline,
 35 1-(1-(3-pyridyl)-5-indolylcarbamoyl)-5-methoxy-6-trifluoromethyl indoline,
 5-Methylthio-6-trifluoromethyl-1-[3-[2-(3-pyridyl)thiazol-4-yl]phenylcarbamoyl]
 indoline,

- 5-Methylthio-6-trifluoromethyl-1-{4-[2-(4-pyridyl)-thiazol-4-yl]phenyl carbamoyl}indoline,
 5-Methylthio-6-trifluoromethyl-1-{4-[2-(3-pyridyl)-thiazol-4-yl]phenylcarbamoyl}indoline,
 5 1-[4-Fluoro-3-(3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[3-Fluoro-5-(pyrimidin-5-yl)phenylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 1-[4-Chloro-3-(4-methyl-3-pyridyl)phenylcarbamoyl]-5-methoxy-6-trifluoromethylindoline,
 10 1-[2,3-Dihydro-7-(pyrid-3-yl)benzofuran-5-ylcarbamoyl]-5-methoxy-6-trifluoromethyl indoline,
 5-Methoxy-6-trifluoromethyl-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 5-Methoxy-6-trifluoromethyl-1-[6-(4-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline,
 15 and pharmaceutically acceptable salts thereof.
8. A compound according to any one of claims 1 to 7 for use in therapy.
9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.
- 20 10. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:
- (a) the coupling of a compound of formula (II);



25

(II)

with a compound of formula (III);

D-R^{4'} (III)

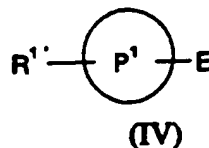
30

wherein A, P¹ and P² are as defined in formula (I), C and D contain the appropriate functional group(s) necessary to form the moiety -NR^{3'}CO when coupled, the variables R^{1'}, R^{2'}, R^{3'} and R^{4'} are R¹, R², R³ and R⁴ respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary
 35 and in any appropriate order, converting any R^{1'}, R^{2'}, R^{3'} and R^{4'}, when other than

R^1 , R^2 , R^3 and R^4 respectively to R^1 , R^2 , R^3 and R^4 , interconverting R^1 , R^2 , R^3 and R^4 and forming a pharmaceutically acceptable salt thereof; or

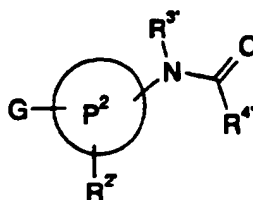
(b) the coupling of a compound of formula (IV);

5



with a compound of formula (V);

10



15

wherein P^1 , P^2 , $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are as defined above and E and G contain the appropriate functional group(s) necessary to form the A moiety when coupled and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1 , R^2 , R^3 and R^4 respectively to R^1 , R^2 , R^3 and R^4 , interconverting R^1 , R^2 , R^3 and R^4 and forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

In national Application No
PCT/EP 96/00368

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/12 A61K31/44 A61K31/40 C07D401/14 C07D417/14
C07D413/12 C07D409/14 C07D403/12 C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 22871 (SMITHKLINE BEECHAM PLC ;FORBES IAN THOMSON (GB); MARTIN ROGER THOM) 13 October 1994 see the whole document ---	1-4,8,9
X	WO,A,94 04533 (SMITHKLINE BEECHAM PLC ;FORBES IAN THOMSON (GB); MARTIN ROGER THOM) 3 March 1994 see the whole document ---	1-4,8,9
X	WO,A,92 05170 (BEECHAM GROUP PLC) 2 April 1992 see the whole document ---	1-4,8,9
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* "&" document member of the same patent family

Date of the actual completion of the international search

24 April 1996

Date of mailing of the international search report

10.05.96

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Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/EP 96/00368

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CROSSFIRE Beilstein XP002001373 BRN=2955290 & DE,A,19 12 553 (CIBA LTD.) 1969 ---</p>	1,2,4
X	<p>DATABASE CROSSFIRE Beilstein XP002001374 BRN=3419367 & JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 79, 1957, DC US, pages 1236-1242, BEAVER ET AL.: ---</p>	1-4
X	<p>DATABASE CROSSFIRE Beilstein XP002001375 BRN=2138496 & TETRAHEDRON LETTERS, 1970, OXFORD GB, page 4905 GRUPON ET AL.: ---</p>	1-4
X	<p>DATABASE CROSSFIRE Beilstein XP002001376 BRN=1159992 & US,A,3 257 204 1958 ---</p>	1-4
X	<p>DATABASE CROSSFIRE beilstein XP002001377 BRN=258176 & SYNTHESIS, 1976, STUTTGART DE, page 40 W. KING: -----</p>	1-4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/00368

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 1-4, 6-8-10 are so broad that a complete search was not possible for economical reasons. Only a few examples of novelty destroying documents have been cited in the search report.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. National Application No

PCT/EP 96/00368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9422871	13-10-94	EP-A- 0691973	17-01-96
WO-A-9404533	03-03-94	AU-B- 4704693	15-03-94
		CA-A- 2142721	03-03-94
		CN-A- 1086819	18-05-94
		EP-A- 0656003	07-06-95
		JP-T- 8500580	23-01-96
		NZ-A- 254785	26-09-95
		SI-A- 9300438	31-03-94
		ZA-A- 9306050	20-02-95
WO-A-9205170	02-04-92	AU-B- 642041	07-10-93
		AU-B- 8503891	15-04-92
		CA-A- 2091246	14-03-92
		EP-A- 0550507	14-07-93
		JP-T- 6500551	20-01-94
		US-A- 5328922	12-07-94